

To explore the mechanism of huangqi guizhi wuwu decoction in the treatment of rheumatoid arthritis based on network pharmacology

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Abstract: objective: to explore and analyze the mechanism of huangqi guizhi wuwu decoction in the treatment of RA by network pharmacology, providing a potentially effective research direction for more basic and clinical studies. Methods: using TCMSP huangqi guizhi wuwu decoction of the effective components of each Chinese medicine and its corresponding target to screen; The RA targets were screened in Genecards, OMIM and Drugbank databases. The therapeutic target of huangqi guizhi wuwu decoction for RA was obtained by using Venny2.1 platform. STRING 11.0 was used to construct the intersection target PPI network and Cytoscape3.7.2 software was used to generate the TCM - compound component - target - disease network diagram. The Metascape platform was used to carry out GO enrichment analysis and KEGG pathway enrichment analysis on the intersection targets. The first 20 pathways of KEGG pathway enrichment analysis were screened and the "target-pathway" network diagram was constructed through Cytoscape3.7.2. Results: huangqi guizhi wuwu decoction on 26 effective active ingredient of RA and 123 targets, such as propagated, IL6, AKT1, TNF, VEGFA, TP53, participated in the AGE of diabetes complications - RAGE signaling pathways, cancer related pathways, the nf-kappa B signaling pathway and PI3K - Akt signaling pathways, such as endocrine resistance to multiple pathways. Conclusion: huangqi guizhi wuwu decoction may be used to treat RA by inhibiting inflammatory response, regulating immune function and regulating apoptosis pathways.

1. Background

Rheumatoid arthritis is essentially a systemic autoimmune disease that mainly involves surrounding joints, and is characterized by symmetric polyarthritis [1]. The clinical manifestations are mainly morning stiffness, joint swelling and pain, cartilage destruction and joint space narrowing, which eventually lead to joint deformity, rigidity and dysfunction, and make the patient incapacitated or even disabled [2]. The prevalence of RA in my country is about 0.28% lower than that in developed countries, and there are more than 4 million patients, of which more women have more than men [3].

The current drug treatments for RA are mainly divided into non-steroidal anti-inflammatory drugs, slow-acting antirheumatic drugs and immunosuppressants, glucocorticoids, immune and biological treatments, and botanical treatments [4, 5].

Huangqi Guizhi Wuwu Decoction is a traditional Chinese medicine decoction composed of astragalus, cassia twig, white peony root, ginger, and jujube. It has a significant effect on the treatment of RA. The cause of RA is insufficient righteousness and exogenous evils. , And the effect of Huangqi Guizhi Wuwu Decoction is mainly based on invigorating Qi and warming Yang and dredging collaterals. Its treatment principle is to consolidate the body and promote the yuan and eliminate wind and cold. Therefore, RA can be treated by adding and subtracting Huangqi Guizhi Wuwu Decoction [6, 7, 8].

At present, there are few reports on the specific mechanism of Huangqi Guizhi Wuwu Decoction in the treatment of RA. In order to clarify its mechanism of action, this study uses network pharmacology to explore and analyze the mechanism of Huangqi Guizhi Wuwu Decoction in the treatment of RA. Basic research and clinical research provide potentially effective research directions.

2. Materials and methods

2.1 Screening of target genes related to Huangqi Guizhi Wuwu Decoction

From the TCM system pharmacology database and analysis platform TCMSP (<http://lsp.nwu.edu.cn/tcmsp.php>), search for various Chinese medicines (astragalus, cassia twig, white peony, ginger) in Huangqi Guizhi Wuwu Decoction , Jujube), the setting parameters of oral bioavailability (OB) $\geq 30\%$, drug-like properties (DL) ≥ 0.18 , to obtain the compound components of five drugs in HQGZWWT. Enter the compound composition in the database to obtain its corresponding target.

2.2 Screening of rheumatoid arthritis related targets

Use "Rheumatoid Arthritis" as the search term to search in 3 disease databases: Genecards (<https://genecards.weizmann.ac.il/v3/>), OMIM (<http://omim.org/>), Drugbank (<https://www.drugbank.ca/>), import the retrieved protein targets into Excel to record and eliminate duplicate information to obtain rheumatoid arthritis-related targets.

2.3 The intersection of Chinese medicine and disease target genes

Through the Venny2.1 platform (<https://bioinfogp.cnb.csic.es/tools/venny/index.html>), the target points of the effective active ingredients of Huangqi Guizhi Wuwu Decoction and the disease targets of rheumatoid arthritis are intersected, Obtain the Venn diagram of the common target genes of traditional Chinese medicine-disease, from which the effective ingredients and target protein genes of Huangqi Guizhi Wuwu Decoction for the treatment of RA are obtained.

2.4 Adding the target gene name (gene symbol)

Use Uniprot database (<http://www.uniprot.org/>) to convert the obtained intersection target protein name into the corresponding target protein gene name. Because individual targets cannot get matching gene names in the UniProt database, they are deleted, so the actual target gene names are fewer.

2.5 Construction of Interaction Network (PPI) between Intersection Target Proteins

Import the obtained intersection target into STRING 11.0 (<https://string-db.org/>) and set the protein

type to "homo sapiens", save the corresponding result file to obtain the PPI network diagram of the intersection target.

2.6 Construction of Traditional Chinese Medicine-Compound Ingredients-Target-Disease Network

According to Cytoscape 3.7.2 software (<http://www.cytoscape.org/>), upload the target information of Huangqi Guizhi Wuwu Decoction Chinese medicine and RA intersection to generate a network diagram of Chinese medicine-compound components-target-disease. Set the nodes of diseases, traditional Chinese medicines, compound components and targets to different colors, and set the node size by the Degree value.

2.7 Enrichment analysis of signal pathways

The common target genes of traditional Chinese medicine and disease were analyzed through the Metascape platform (<http://metascape.org>) for GO function enrichment analysis and KEGG pathway enrichment analysis. Select the biological process (Biological Process), molecular function (Molecular Function) and cellular component (Cellular Component) in GO function for gene enrichment analysis, using the WeChat platform (<http://www.bioinformatics.com.cn/>) Perform KEGG pathway enrichment analysis and GO function enrichment analysis on the intersection targets, and the results are visualized by KEGG enrichment bubble chart and GO function enrichment analysis BP, CC, MF three-in-one histogram.

2.8 Target-path network construction

Screen the top 20 pathways of KEGG pathway enrichment analysis in 1.7 by Log₁₀(P) value, find out the targets of Huangqi Guizhi Wuwu Decoction in the treatment of RA enrichment on these pathways, and use Cytoscape 3.7.2 to construct after integrating the data." Target-pathway" network relationship diagram.

3. Results

3.1 Screening of active ingredients and related targets of traditional Chinese medicine and disease-related targets

Through the screening of all the reported active ingredients and related targets of each Chinese medicine in Huangqi Guizhi Wuwu Decoction in the TCMSP database, the active ingredients of *Drynaria fortunei* were screened according to the OB and DL parameters. After the duplicates were eliminated, a total of effective ingredients were obtained. There are 42 ingredients and 229 targets corresponding to the effective ingredients. Through the screening of Genecards (due to too much data, the card value was performed twice by the median), OMIM, and Drugbank database, duplicate information was eliminated, and 1,292 rheumatoid arthritis-related targets were obtained.

3.2 The intersection of TCM target genes and disease target genes

Through the Venny2.1 platform, the target of the effective active ingredients of traditional Chinese medicine and the RA disease target are intersected, and the Venn diagram of the common target genes of traditional Chinese medicine-disease is obtained (see Figure 1), of which 1292 RA target genes, Huangqi Guizhi There are 229 target genes in Wuwutang. 123 common target genes of traditional Chinese medicine-disease were obtained from this, and the 26 compound components contained in

Huangqi Guizhi Wuwu Decoction were matched through the intersection of target genes (see Table 1).

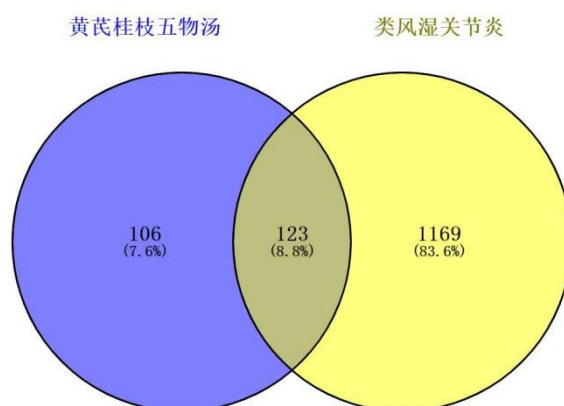


Figure 1: Intersection of TCM target genes and disease target genes

Table 1: List of active ingredients of Huangqi Guizhi Wuwu Decoction acting on RA

MOLID	中文名	英文名	OB	DL
MOL000098	槲皮素	quercetin	46.43	0.28
MOL000211	迈林	Mairin	55.38	0.78
MOL000239	佳罗醇	Jaranol	50.83	0.29
MOL000296	赫达拉汀	hederagenin	36.91	0.75
MOL000354	异鼠李素	isorhamnetin	49.6	0.31
MOL000371	3,9-di-O-methylnissofin	3,9-di-O-methylnissofin	53.74	0.48
MOL000378	7-O-甲基异丁香酚	7-O-methylisomucronulatol	74.69	0.3
MOL000380	(6aR, 11aR) -9	(6aR,11aR)-9	64.26	0.42
MOL000387	联苯双酯	Bifendate	31.1	0.67
MOL000392	福莫宁	formononetin	69.67	0.21
MOL000422	山柰酚	kaempferol	41.88	0.24
MOL000358	β -谷甾醇	beta-sitosterol	36.91	0.75
MOL000492	(+) -儿茶素	(+)-catechin	54.83	0.24
MOL001736	(-) -紫杉酚	(-)-taxifolin	60.51	0.27
MOL004576	滑石粉	taxifolin	57.84	0.27
MOL001919	(3S, 5R,8R, 9R, 10S, 14S) -3	(3S,5R,8R,9R,10S,14S)-3	43.56	0.53
MOL001924	芍药苷	paeoniflorin	53.87	0.79
MOL000449	豆甾醇	Stigmasterol	43.83	0.76
MOL000787	富马林	Fumarine	59.26	0.83
MOL001454	小檗碱	berberine	36.86	0.78
MOL001522	(S) -牛尿蛋白	(S)-Coclaurine	42.35	0.24
MOL002773	β -胡萝卜素	beta-carotene	37.18	0.58
MOL007213	核素	Nuciferin	34.43	0.4
MOL012921	光千金藤碱	stepharine	31.55	0.33
MOL012976	香豆酚	coumestrol	32.49	0.34
MOL006129	6-甲基乙酸二甲酯	6-methylgingediacetate2	48.73	0.32

3.3 Construction of Interaction Network (PPI) between Intersecting Target Proteins

The obtained intersection targets were imported into the STRING 11.0 platform for drawing, and the target PPI network of Huangqi Guizhi Wuwu Decoction and RA was obtained (see Figure 2), including 123 main nodes and 2416 edges. Among them, the adjacent nodes are more the six more targets are: ALB, IL6, AKT1, TNF, VEGFA, TP53.

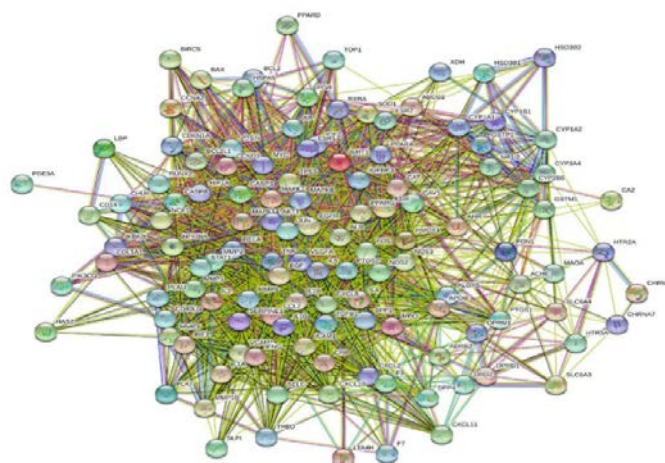


Figure 2: List of active ingredients of Huangqi Guizhi Wuwu Decoction acting on RA

3.4 Construction of Traditional Chinese Medicine-Compound Components-Target-Disease Network

Use Cytoscape 3.7.2 software to construct a network of traditional Chinese medicine-compound components-targets-disease (see Figure 3). The red circle in the figure represents RA, and the green octagon represents the five traditional Chinese medicines contained in Huangqi Guizhiwu Wuwu Tang, and the blue arrow Represents the components of the compound, and the yellow diamond represents the intersection target. Huangqi Guizhi Wuwu Decoction mainly acts on 123 target genes by intersecting 26 active ingredients matched by target genes. These 123 target genes may have an impact on the treatment of RA. By setting the node size by the Degree value, it can be seen that the effective ingredient of Huangqi Guizhi Wuwu Decoction is closely related to the treatment of RA is quercetin, kaempferol, beta-sitosterol, Taxifolin etc.

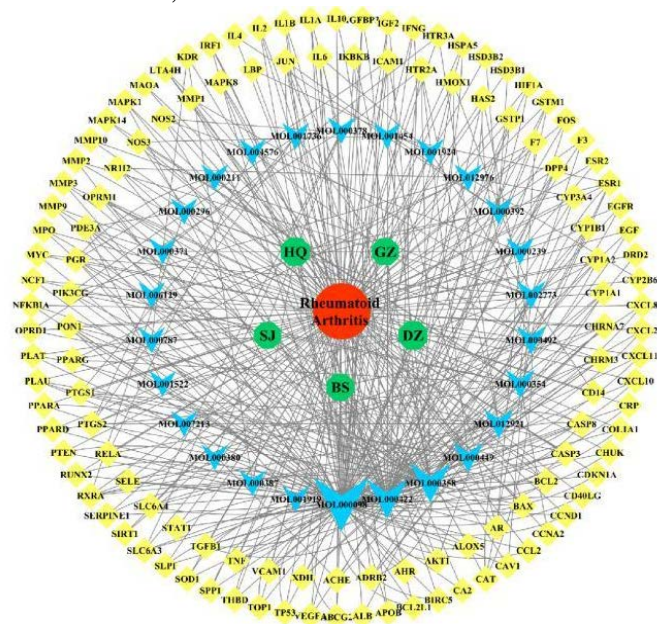


Figure 3: TCM - compound composition - target - disease network

functional enrichment analysis results obtained by running on the Metascape platform showed that the large number of genes enriched in GO biological processes are cytokine-mediated signaling pathways, response to toxic substances, response to lipopolysaccharides, etc.; GO cells are enriched in groups The larger number of genes include membrane rafts, vesicle cavity, extracellular matrix, etc.; the larger number of GO molecular functional enrichment genes include protein homodimerization activity, transcription factor binding, lipid binding, and so on. (See Figure 5)

3.6 Target-path network construction

The active targets and key signal pathways were imported into Cytoscape 3.7.1 software for visual analysis, and RA-related Huangqi Guizhi Wuwu Decoction was enriched in these pathways to construct a "target-pathway" network relationship diagram (see Figure 6).

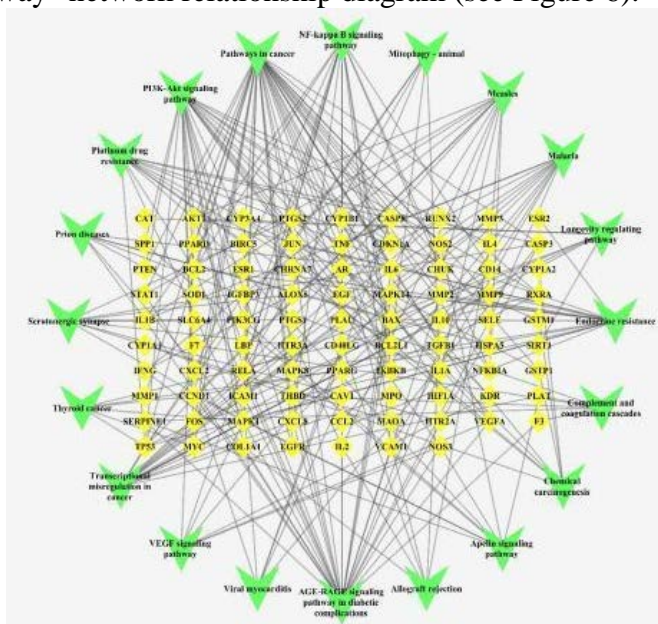


Figure 6: Target - pathway network diagram

4. Discussion

This study is based on the "holistic concept" theory of Chinese medicine and the method of network pharmacology, with the help of related databases and software to explore and analyze the mechanism of Huangqi Guizhi Wuwu Decoction in the treatment of RA. Through data integration and summary, 26 effective active ingredients of Huangqi Guizhi Wuwu Decoction acting on RA and 123 intersecting targets were obtained. By constructing Huangqi Guizhi Wuwu Decoction and RA-related target PPI network, Chinese medicine-compound component-target-disease network, and performing KEGG pathway enrichment analysis and GO function enrichment analysis on related targets, then Huangqigui The mechanism of action of Zhiwuwu Decoction in the treatment of RA was systematically reviewed.

The results of the study show that the effective ingredients of Huangqi Guizhi Wuwu Decoction that are closely related to the treatment of RA include quercetin, kaempferol, β -sitosterol, taxifolin, etc., through literature and database searches, it is found that quercetin can reduce Th17 differentiation, It reduces the expression of a series of proteins that play an important role in the development of RA, and inhibits inflammatory cell infiltration and angiogenesis [9,10,11]; kaempferol acts on the receptor 3-ribosome S6 kinase 2 signal axis fibroblast growth factor receptor

and inflammatory cytokines such as IL-17, IL-21 and TNF- α inhibit the development of RA [12,13,14]; β -sitosterol can affect tumors Cell proliferation and angiogenesis have an inhibitory effect, and it acts on RA by eliminating inflammation [15]; Taxifolin can regulate the NF- κ B signaling pathway in the KEGG pathway enrichment analysis, inhibit the formation of osteoclasts, and promote Differentiation of osteoblasts, thereby reducing bone tissue damage [16]. Through the PPI network of Huangqi Guizhi Wuwu Decoction and RA-related targets, the six targets with the most adjacent nodes are: ALB, IL6, AKT1, TNF, VEGFA, and TP53. These targets may play a key role in the treatment of RA. Effect. RA is a disease related to oxidative stress, and ALB plays an important role in antioxidant defense, so it has a significant impact on the disease activity of chronic inflammatory diseases [17, 18]; IL6 is the main mediator of RA joint damage By inducing the production and release of other inflammatory cytokines to aggravate the inflammatory response, it plays an important role in the immune response of the body; AKT1 belongs to the most important subtype of AKT [19, 20], Xu Ning [21] and others found that Decreasing the expression of AKT can significantly inhibit the proliferation of RA fibroblast-like synovial cells (FLS); TNF has two different receptors. By activating the MAPK and other pathways in FLS, it induces FLS to produce a large number of inflammatory cytokines, and aggravates the inflammatory response. Articular cartilage destruction [22]; VEGFA gene is involved in the angiogenesis process and NF- κ B signaling pathway. The study by Zhang Yu [23] found that VEGFA gene is abnormally expressed in FLS of RA patients, suggesting that it may be involved in the occurrence and development of RA ; TP53 can significantly reduce synovial inflammation and IL-6 levels, and play an important role in RA fibroblast-like synovial cell apoptosis [24, 25]. KEGG pathway enrichment analysis results show that AGE-RAGE signaling pathway, cancer-related pathways, NF- κ B signaling pathway, PI3K-Akt signaling pathway, endocrine resistance pathway and Huangqi Guizhi Wuwu Decoction are the most relevant in the treatment of RA in the treatment of RA Closely, the RAGE receptor in the AGE-RAGE signaling pathway is expressed on many immune cells and has the ability to bind to pro-inflammatory ligands. Blocking the AGE-RAGE signaling pathway will hinder the transmission of central inflammatory signals and lead to the delay of the inflammatory response [26]; Some studies have mutations in the tumor suppressor gene p53 in FLS of RA patients, and the expression level of oncogenes in synovial cells is also increased, which indicates that the aggressiveness of RA FLS may be related to cancer-related pathways [27, 28]; The NF- κ B signaling pathway is closely related to immune and inflammatory responses. By activating the NF- κ B signaling pathway, transcription and secretion of a variety of cytokines cause synovial inflammation and cartilage and bone destruction [29]; Synovial cells in RA patients The PI3K-Akt signaling pathway is abnormally activated, leading to high expression of downstream anti-apoptotic genes. This pathway plays a key role in the proliferation and apoptosis of FLS in RA patients [30]; studies have shown that [31] hypothalamus-pituitary- Glucocorticoid, the end product of the adrenal axis, is the main treatment method for many autoimmune diseases (including RA) due to its effective anti-inflammatory effect, which is closely related to the endocrine resistance pathway. It can be speculated that Huangqi Guizhi Wuwu Decoction may treat RA by inhibiting inflammation, regulating immune function and regulating the mechanism of apoptosis pathway. These data indicate that they play a key role in the treatment of RA with Huangqi Guizhi Wuwu Decoction and have potential research value, and provide strong evidence for the prediction results of this study.

In summary, this study used the method of network pharmacology to systematically study the relationship between the components, targets, pathways of Huangqi Guizhi Wuwu Decoction and RA disease, and unearthed the common target of Huangqi Guizhi Wuwu Decoction-RA 123. Through the KEGG pathway enrichment analysis and GO function enrichment analysis of these targets, the main effective components of Huangqi Guizhi Wuwu Decoction for the treatment of RA and their targets and related pathways are preliminarily clarified. The treatment of RA with decoction has the

characteristics of multiple targets and multiple pathways, and its results can be used as clues for experimental research, providing potentially effective research directions for more basic research and clinical research.

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