Elucidating the Bioactive Compounds and Integrative Strategies of Qibai Powder for Multi-Target Intervention in Melasma

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Abstract. Objective: To investigate the active components and mechanisms of action of Qibai Powder in treating melasma. **Methods:** Screening of drug active components was conducted using the TCMSP and HERB databases, combined with the GeneCards database to obtain disease targets. An intersection of targets was used to construct a protein-protein interaction (PPI) network diagram, followed by Gene Ontology (GO) functional enrichment and KEGG pathway enrichment analysis. Molecular docking between core components and key targets was performed using AutoDock vina software. **Results:** Twenty-five active components were identified, acting on 290 disease targets. Pathway enrichment analysis indicated Qibai Powder primarily mediates cancer pathways, lipid metabolism, and therosclerosis by regulating targets such as TP53 and ESR1. Molecular docking revealed high affinity between key targets and core components. **Conclusion:** Qibai Powder exerts therapeutic effects on melasma through multi-component, multi-target, and multi-pathway mechanisms; however, specific action mechanisms require further validation.

Keywords: Qibai Powder; Melasma; Network Pharmacology; Signaling Pathways; Multi-Target Regulation.

1. Introduction

Melasma, also known as chloasma or pregnancy mask, is a common hyperpigmentation disorder. It primarily manifests as yellowish-brown or coffee-colored pigmented patches on the cheeks0. Melasma predominantly affects young to middle-aged women, characterized by prolonged treatment cycles and high recurrence rates[2]. Its development is associated with multiple factors including genetic predisposition, ultraviolet exposure, and fluctuations in sex hormone levels[3]. Although not life-threatening, melasma negatively impacts patients' facial aesthetics, mental health, and quality of life.

Traditional Chinese Medicine (TCM) offers extensive theoretical foundations and practical experience in treating melasma, primarily guided by the principles of soothing the liver, nourishing blood, promoting blood circulation, and resolving stasis[4]. Qibai Powder, originating from the Yuan Dynasty text Yonglei Qianfang, comprises Atractylodes macrocephala, Angelica dahurica, Poria cocos, Bletilla striata, Bombyx batryticatus, Typhonium giganteum, and Ampelopsis japonica. It is known for beautifying the complexion and brightening the skin[5]. However, due to its numerous herbal constituents and complex chemical composition, existing research lacks a systematic elucidation of its mechanism of action in melasma through a "multi-component-multi-target-multi-pathway" synergistic network intervention.

Therefore, this study employs network pharmacology analysis to systematically screen key active components and their targets in Qibai Powder. By constructing a "drug-component-target" interaction network and integrating protein interaction analysis with pathway enrichment, we delve into core targets and signaling pathways to reveal the mechanism by which Qibai Powder modulates melasma through multi-target synergistic regulation. The findings not only provide scientific support for the clinical application of Qibai Powder but also lay a theoretical foundation for innovative drug development based on its active components.

2. Methods

2.1 Screening of Active Components and Target Identification in Qibai Powder

The TCMSP database (https://tcmsp-e.com/) and the Herb database (http://herb.ac.cn/) were used to screen for effective components using the keywords “Atractylodes macrocephala”, “Angelica dahurica”, “Bletilla striata”, “Typhonium giganteum”, “Cynanchum wilfordii”, “Poria cocos” and “Bombyx batryticatus”. The screening criteria were oral bioavailability (OB) ≥30% and drug-like properties (DL) ≥0.18[6]. Target prediction was performed using the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), the Comparative Toxicogenomics Database (http://ctdbase.org/) and the Swiss Target Prediction Database (http://www.swisstargetprediction.ch/). Non-human genes and invalid duplicate targets were excluded to obtain standardised component-target pairs.

2.2 Collection of Melasma Targets

Using the GeneCards database, search results for the keyword 'melasma' were consolidated and deduplicated. These were then validated against the UniProt database (https://www.uniprot.org/) to disease targets information associated with melasma[7].

2.3 Prediction of Anti-Melasma Targets for Active Components in Qibai San

A Venn diagram was generated using Venny 2.1.0 (https://bioinfogp.cnb. csic.es/tools/ venny /index.html) by inputting the obtained drug component targets and disease targets to identify intersecting genes. We then performed association analysis among the drug, active components, intersecting targets and disease using Cytoscape 3.9.1 software to construct a 'drug-ingredient-target-disease' network diagram[8].

2.4 PPI Network Construction and Core Target Screening

Import the intersecting targets into the STRING database (https://string-db.org/). Set the species to 'human' and the minimum confidence threshold to >0.7 to construct the protein interaction network. Import this network into Cytoscape 3.9.1 for topological analysis and visualisation. Use the CytoHubba plugin to screen and rank targets based on degree values[9].

2.5 GO Functional and KEGG Pathway Enrichment Analysis

Upload the filtered intersection targets to the Metascape database (http://metascape.org/ gp/index. html) for GO and KEGG enrichment analysis[10], with the species set to 'human' and the P-value set to <0.05. Relevant data were uploaded to the WeBioinformatics platform (https://www. bioinformatics. com.cn/) to generate bar charts and Sankey bubble diagrams.

2.6 Molecular Docking

Perform molecular docking between the top three active components from the 'drug–active ingredient–target' diagram and the target proteins screened from the PPI network. Download the compound files in SDF format from the PubChem database and convert them to PDB format. Download the three-dimensional structures of the corresponding target proteins from the PDB database. Use AutoDock Tools-1.5.6 software for dehydration, hydrogenation and other processing steps. Active site docking was then performed using AutoDock, and binding energies were calculated using the AutoDock Vina algorithm. Finally, visualise the molecules using PyMOL software[11] to generate 3D interaction diagrams.

3. Results

3.1 Prediction Results of Active Ingredients and Targets

A total of 25 active ingredients of Qibai Powder were retrieved from the TCMSP database, including 1 from Atractylodes macrocephala, 8 from Angelica dahurica, 1 from Bletilla striata, 3 from Typhonium giganteum, 4 from Ampelopsis japonica, 1 from Poria cocos, and 7 from Bombyx batryticatus. Target prediction was performed using three databases, including PubChem, and after integration and deduplication, 7,922 potential targets were obtained.

3.2 Prediction Results of Disease Targets

A total of 350 potential targets related to melasma were obtained by searching the GeneCards database. After taking the intersection between the drug action targets and the melasma target genes, a Venn diagram was plotted on the bioinformatics platform, resulting in 290 overlapping targets, as shown in Figure 1.

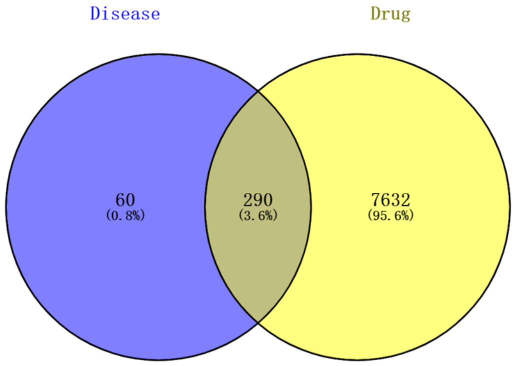

Fig 1. Venn diagram of drug-disease overlapping targets

3.3 Network Construction Results

The "Drug-Components-Overlapping Targets-Disease" network diagram was constructed using Cytoscape 3.7.2 software, as shown in Figure 2, comprising a total of 102 nodes and 143 edges. Topological analysis of this network revealed that the top five compounds ranked by degree value were: quercetin, (+)-catechin, cholesterol, palmitic acid, and ergosterol. These five compounds can interact with the majority of the disease targets and may represent the key active substances responsible for the efficacy of Qibai Powder in treating melasma, thus identifying them as potential core components.

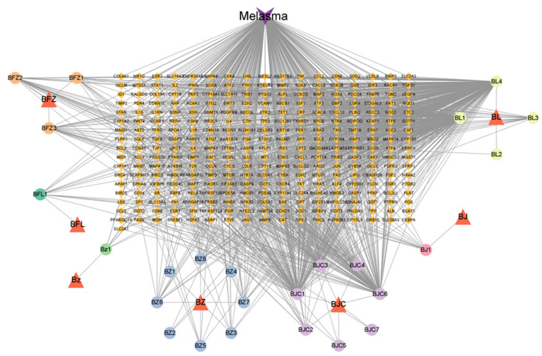

Fig 2. "Drug-Components-Overlapping Targets-Disease" Network Diagram

3.4 Protein-Protein Interaction (PPI) Network Construction Results

The overlapping target genes were imported into the STRING database to construct a protein-protein interaction (PPI) network, which comprised 288 nodes and 147 edges, as shown in Figure 3. The top 18 key targets, ranked by degree value, were identified as: TP53, ESR1, RELA, JUN,

CDKN1A, AKT1, SFN, MAPK8, MAPK1, CASP9, MAPK14, SP1, PIK3R1, CDK4, BCL2L1, BCL2, and FOS. These were considered as the potential core targets through which Qibai Powder regulates melasma.

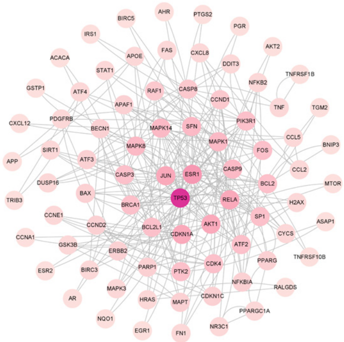

Fig 3. Protein-Protein Interaction (PPI) Network

3.5 Results of Biofunctional Enrichment Analysis

3.5.1 GO Enrichment Analysis Results

The overlapping targets were analyzed using the Metascape database. A total of 439 GO functional enrichment terms were screened, encompassing 562 biological processes (BP), 189 cellular components (CC), and 330 molecular functions (MF). The top 10 processes from each category, ranked by p-value, were selected for visualization, as shown in Figure 4. The biological processes primarily involved response to nutrient levels, cellular response to cytokine stimulus, regulation of phosphorylation, positive regulation of programmed cell death, and cellular response to lipid. The cellular components included the perinuclear region of cytoplasm, endoplasmic reticulum lumen, transcription regulator complex, secretory granule lumen, and collagen-containing extracellular matrix. The molecular functions were mainly associated with kinase binding, transcription factor binding, protein homodimerization activity, receptor ligand activity, and oxidoreductase activity.

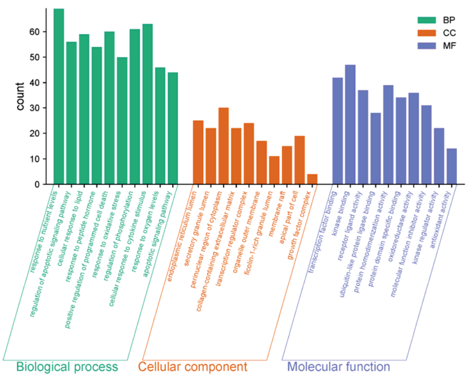

Fig 4. GO Functional Enrichment Analysis Results

3.5.2 KEGG Pathway Enrichment Analysis Results

Utilizing the Metascape database, a total of 131 KEGG pathways were screened. These were primarily associated with pathways in cancer, lipid and atherosclerosis, neurodegeneration-multiple diseases pathway, Kaposi sarcoma-associated herpesvirus infection, and fluid shear stress and atherosclerosis. Based on p-value ranking, the top 10 enriched pathways were selected to generate a Sankey bubble diagram, as shown in Figure 5. In the left section of the chart, the first column represents genes, the second column represents enriched pathways, and the thickness of the connecting lines indicates the strength of the association between the targets and pathways, with each node representing a specific pathological process. In the right section, the x-axis represents the number of genes enriched in a pathway, the y-axis represents the enriched pathways, the bubble size corresponds to the number of genes in the pathway, and the color intensity indicates the p-value, with darker red representing smaller (more significant) p-values.

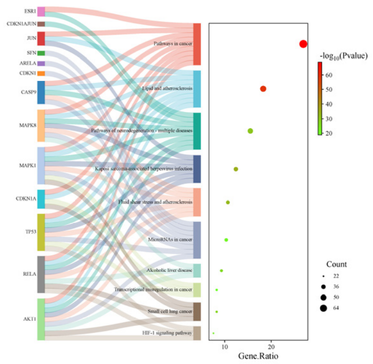

Fig 5. Sankey Bubble Diagram of KEGG Pathway Enrichment

3.6 Molecular Docking Results

Molecular docking was performed between the core components and the core targets, with the results shown in Table 1. The binding energies for all component-target pairs were less than -5 kcal/mol, indicating favorable binding. The top three results, ranked by binding energy, were visualized using PyMOL software, as shown in Figures 6-8.

Table 1. Binding Energies of Active Ingredients with Key Targets

Compound Name	Binding Energy(KJ/mol)				
	TP53	ESR1	RELA	JUN	CDKN1A
quercetin	-7.2	-8.6	-9.2	-8.2	-7.2
(+)-catechin	-7.6	-9.3	-8.4	-8.3	-7.2
cholesterol	-7.1	-9	-9	-7.6	-8.4
palmitic acid	-4.6	-6.5	-5.6	-5.7	-5
ergosterol	-7.5	-9.5	-9.6	-10.6	-8.4

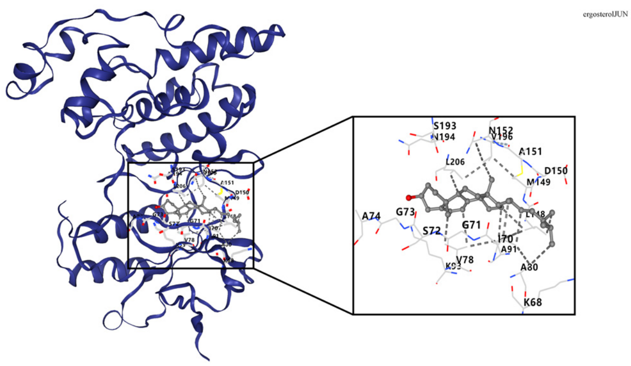

Fig 6. Molecular Docking Diagram of Ergosterol with JUN

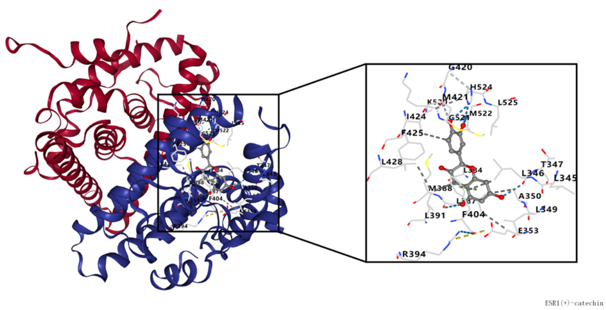

Fig 7. Molecular Docking Diagram of (+)-Catechin with ESR1

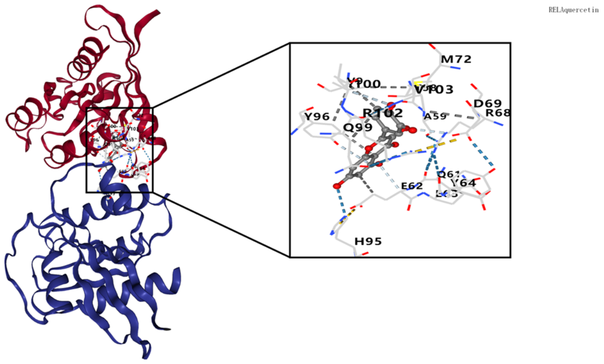

Fig 8. Molecular Docking Diagram of Quercetin with RELA

4. Summary

This study systematically elucidates, through network pharmacology and molecular docking technology, the potential mechanism by which the core active ingredients of Qibai Powder intervene in melanin synthesis and metabolism-related pathways via the synergistic regulation of key targets such as TP53 and ESR1. This provides a theoretical foundation for the clinical application and development of this classic formulation.

The active component screening results indicate that five core components, including quercetin and catechin, constitute the key material basis for the efficacy of Qibai Powder. Among these, quercetin, a typical flavonoid compound, has been confirmed to possess significant anti-inflammatory and antioxidant activities. It can scavenge free radicals to mitigate oxidative stress damage to melanocytes and inhibit the expression of key enzymes in melanin synthesis, such as tyrosinase[12]. Catechin, a natural polyphenol, not only regulates heme oxygenase activity to enhance the cellular antioxidant defense system but also inhibits the transfer of melanosomes to keratinocytes[13]. This aligns with the high-affinity binding results with ESR1 observed in our study.

Analysis of disease targets reveals that the intervention of Qibai Powder in melasma is primarily associated with targets such as TP53, ESR1, and JUN. The main functions of TP53 include DNA synthesis and repair, regulation of cell senescence and apoptosis, and inhibition of cancer cell proliferation[14]. In melanocytes, it can regulate the cell cycle, reducing ultraviolet-induced genomic damage and abnormal proliferation. As an estrogen receptor, ESR1 binding promotes pigment synthesis in melanocytes[15]. The high-affinity binding of core components with ESR1 observed in our study suggests that these components may block this pathological process through competitive inhibition. JUN can be phosphorylated and activated under stimulation by inflammatory factors and ultraviolet radiation[16], thereby promoting the expression of various melanogenesis-related genes. Its high affinity with the core components provides direct evidence for the efficacy of Qibai Powder in ameliorating pigmentation.

GO and KEGG pathway enrichment results further clarify the mechanism of multi-pathway synergistic regulation by Qibai Powder. Enrichment in cancer pathways suggests that the core components may reduce abnormal proliferation and survival of melanocytes. Enrichment in lipid and atherosclerosis pathways indicates that Qibai Powder may exert its effects by improving vascular endothelial function. Modern medical research has shown that melasma patients often exhibit local skin microcirculation disorders, characterized by increased plasma viscosity and accumulation of metabolic products[17]. The pharmacological mechanism associated with this pathway may be related to the traditional efficacy of Qibai Powder in "promoting blood circulation and resolving stasis." The significance of the neurodegeneration-multiple diseases pathway corresponds to the clinically observed phenomenon that mental stress may exacerbate melasma[18].

In summary, this study reveals that Qibai Powder, through core components such as quercetin and catechin, targets and regulates key nodes including TP53 and ESR1, synergistically intervening in multiple pathological processes such as melanin synthesis, oxidative stress, and inflammatory responses. These findings provide experimental evidence for its clinical application and offer insights for innovative drug development based on classic formulations.

Acknowledgments

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