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Exploring the Mechanism of Coptis Chinensis in Improving Myocardial Fibrosis Based on Network Pharmacology

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Abstract: *This study utilized network pharmacology methods to explore the main active components and intervention targets of Coptis chinensis in influencing myocardial fibrosis, to clarify its mechanism of action. The main active components and their target genes were retrieved from the TCMSP network pharmacology database and the Swisstargetprediction platform. Target genes associated with myocardial fibrosis were identified via the Genecards and OMIM databases. Cytoscape 3.10 software was employed to construct a network diagram connecting traditional Chinese medicine, active components, and gene targets. A protein-protein interaction (PPI) network was generated in the String database to calculate target degree values. Analysis using the Metascape database was conducted on Gene Ontology (GO) functional enrichment and KEGG pathway enrichment analyses on the targets. A total of 14 major active components and 130 drug-related targets were identified from Coptis chinensis. Targets associated with myocardial fibrosis were obtained from the Genecards database (16,227) and the OMIM database (68). After target intersection, 130 potential therapeutic targets were identified, with key genes including TNF, AKT1, SRC, EGFR, and PTGS2. GO and KEGG enrichment analyses indicated that Coptis exerts therapeutic effects on myocardial fibrosis through biological processes including positive regulation of cell migration, cell motility and locomotion, cellular response to nitrogen compounds, and regulation of the MAPK cascade, as well as pathways such as the PI3K-Akt signaling pathway. Coptis holds promise in treating myocardial fibrosis by functioning via a multi-target and multi-pathway regulatory network that impacts cardiac metabolism.*

Keywords: *Myocardial Fibrosis; Network Pharmacology; Coptis Chinensis; Traditional Chinese Medicine*

1. Introduction

Myocardial fibrosis (MF) is characterized by the excessive activation of cardiac fibroblasts and the abnormal deposition of extracellular matrix, ultimately leading to the progressive deterioration of cardiac structure and function[1][2]. It represents a common terminal pathological change in various cardiovascular diseases. Although conventional therapies centered on renin - angiotensin - aldosterone system inhibitors are widely used in clinical practice, there remains an urgent need to pursue more effective strategies to delay or reverse the progression of fibrosis[3][4]. Against this backdrop, the traditional Chinese medicine Coptis chinensis, with its multi-component and multi-targeted action profile, offers a potential new avenue for intervening in this complex pathological process. Modern pharmacological studies have revealed that the rhizome of Coptis chinensis contains a diverse array of bioactive compounds beyond berberine, including quercetin, (R)-coptisine, phellodendrine, and various coptisine-type alkaloids[5]. These constituents may synergistically exert protective effects on the cardiovascular system through multiple mechanisms, such as anti-inflammatory action, antioxidant stress relief, and the regulation of cellular signaling pathways[6][7]. Network pharmacology prediction analysis suggests that the key bioactive components in Coptis may exert protective effects against ischemic heart disease by targeting core pathways, including interleukin 6, tumor necrosis factor, protein kinase B1, fluid shear stress, atherosclerosis, and advanced glycation end-product receptors. This provides indirect evidence for Coptis chinensis' potential intervention in fibrosis-related diseases[8]. Therefore, employing network pharmacology—an emerging strategy integrating systems biology, bioinformatics, and pharmacology—to systematically investigate its mechanism against myocardial fibrosis holds significant scientific value. This approach enables a multidimensional network-level analysis spanning “drug - component - target -

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pathway - disease," holistically revealing how multiple active constituents in Coptis chinensis synergistically regulate critical stages of myocardial fibrosis. These include inhibiting the release of pro-fibrotic factors, modulating cardiac fibroblast activation and proliferation, and balancing extracellular matrix synthesis and degradation[9]. This approach not only overcomes the limitations of traditional single-target research but also elucidates the therapeutic characteristics of Coptis chinensis—its "multicomponent, multitarget, and multipathway" properties. Furthermore, it provides a robust theoretical foundation and a clear functional network map for developing Coptis chinensis into an innovative anti-myocardial fibrosis drug[10].

2. Materials and Methods

2.1 Software and Databases

This study utilized Cytoscape 3.10 software. The databases included the TCMSP database (https://old.tcmsp-e.com/tcmsp.php), the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), SwissTargetPrediction (https://www.swisstargetprediction.ch/), GeneCards (https://genecards.org/), OMIM (https://omim.org/), UniProt (http://www.uniprot.org/), Venny 2.2.0 (https://bioinfogp.cnb.csic.es/tools/venny/), STRING (https://cn.string-db.org/), Metascape (https://metascape.org/), and the Microletter online website (http://www.bioinformatics.com.cn/login/). The software was run on a 64-bit Windows 10 system.

2.2 Identification of Active Components and Targets in Coptis

Active components related to Coptis were identified by searching the TCMSP (Traditional Chinese Medicine System Pharmacology Database and Analysis Platform) database. The active components were screened according to the criteria of oral bioavailability (OB) ≥ 30% and drug similarity (DL) ≥ 0.18. The corresponding standardized chemical formulas were searched in the PubChem database. Finally, these standardized chemical formulas were input into the Swiss-TargetPrediction platform, with the species restricted to Homo sapiens. Target proteins were selected based on probability values greater than 0 to identify the corresponding target genes for the qualified active components. After removing duplicate targets, a list of predicted targets for the effective active components of Coptis chinensis was obtained. 、

2.3 Screening of Myocardial Fibrosis-Related Targets

Target genes for myocardial fibrosis were retrieved using the keyword "Myocardial fibrosis" in the GeneCards and OMIM databases. The screening criteria for each database were as follows: In GeneCards, drug-target relevance was determined by the median of the second-order correlation. In both GeneCards and OMIM, drug and target categories were restricted to humans. After merging and removing duplicates, this constituted the myocardial fibrosis dataset. Venny 2.2.0 processed the myocardial fibrosis and Coptis chinensis gene datasets, generating a Venn diagram to identify their shared core targets.

2.4 Construction of Protein-Protein Interaction (PPI) Network

The selected core genes were input into the STRING database to obtain corresponding protein-protein interaction (PPI) data. Subsequently, the PPI data were imported into Cytoscape 3.10 software for visualization, which enables more intuitive analysis and understanding of the relationships among these proteins.

2.5 Functional Enrichment Analysis of Core Targets

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were conducted using the Metascape and KEGG databases. GO classifications covered multiple dimensions, including biological processes (BP), cellular components (CC), and molecular functions (MF). Enrichment results were filtered with a threshold of $P < 0.05$. The top 10 entries from BP/CC/MF and the top 20 entries from KEGG were chosen for visualization in statistical charts.

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3. Results

3.1 Identification of Active Components and Targets in Coptis

Preliminary screening criteria in the TCMSP database were set as: OB%（oral bioavailability）≥ 30 and DL（drug-likeness) ≥ 0.18, yielding 14 active components associated with Coptis (Table 1).

Table 1: Active components of coptidis rhizoma

Mol ID	Molecule Name	OB (%)	DL
MOL001454	berberine	36.86	0.78
MOL013352	Obacunone	43.29	0.77
MOL002894	berberrubine	35.74	0.73
MOL002897	epiberberine	43.09	0.78
MOL002903	(R)-Canadine	55.37	0.77
MOL002904	Berlambine	36.68	0.82
MOL002907	Corchoroside A_qt	104.95	0.78
MOL000622	Magnograndiolide	63.71	0.19
MOL000762	Palmidin A	35.36	0.65
MOL000785	palmatine	64.6	0.65
MOL000098	quercetin	46.43	0.28
MOL001458	coptisine	30.67	0.86
MOL002668	Worenine	45.83	0.87
MOL008647	Moupinamide	86.71	0.26

3.2 Target Sites of Active Components in Coptis

The relevant active components of Coptis were input into the Swisstargetprediction platform to obtain the names of drug targets. Target genes with P > 0 were selected. The target genes corresponding to the active components of Coptis were imported into the UniProt database for gene normalization. After removing duplicates, a total of 442 predicted target genes for the active components of Coptis were identified.

3.3 Myocardial Fibrosis-Related Targets

Using the keyword “Myocardial fibrosis,” 5,349 and 68 relevant targets were retrieved from the Genecards and OMIM databases, respectively. A secondary median value was applied to the targets from the Genecards database. After removing duplicates, 1,357 myocardial fibrosis-related targets were obtained. By comparing the 422 predicted targets of the active components in Coptis chinensis with the myocardial fibrosis-related targets, 130 overlapping targets were identified. Using the Venny 2.2.0 online software for mapping, we input the chemical constituents and MF target genes separately. Subsequently, a Venn diagram was generated to identify the common targets between the active constituents and MF (Figure 1).

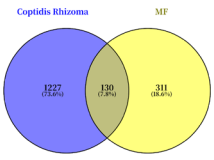

Figure 1: Screening Results of Myocardial Fibrosis-Related Targets

3.4 Visualization of the Relationship between Major Active Components of Coptis and Their Targets

After importing the data on major active components of Coptis and their corresponding targets (Table

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1) into Cytoscape 3.10 software, a visual network was constructed to illustrate the interaction relationships between the active components of Coptis and their targets. In this network, each node represents Coptis, its active components, or relevant targets associated with myocardial fibrosis (MF). Connections between nodes reveal interactions among these entities. As depicted in Figure 2 this network diagram illustrates the multi-target mechanisms through which the active components of *Coptis chinensis* interact with specific targets to influence myocardial fibrosis.

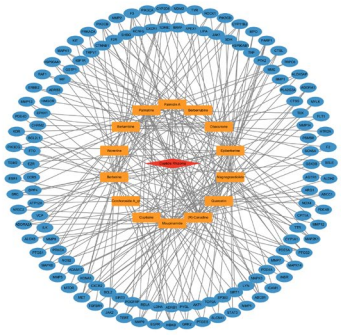

Figure 2: Network Results of Coptis-Active Components-Targets- Myocardial Fibrosis

3.5 Potential Target Protein-Protein Interaction (PPI) Network Analysis

To further investigate the therapeutic mechanism of Coptis chinensis against myocardial fibrosis, we imported all 130 common targets into the STRING database for protein-protein interaction (PPI) network analysis. As shown in Figure 3, this PPI network consists of 130 nodes and 1,873 edges, indicating complex interaction relationships. The average degree value of this protein network is 28.8, with a local clustering average coefficient of 0.58. As shown in Figure 4, the TSV file imported from the STRING database was loaded into Cytoscape 3.10. Node color intensity represents the target's Degree Centrality, while node size reflects the target's Betweenness Centrality. The results indicate that the genes AKT1, TNF, PTGS2, and TP53 have the highest degree values, highlighting their significance. These may represent key therapeutic targets for MF, offering novel potential directions for treatment. The top 20 genes ranked by Degree Centrality and Betweenness Centrality were selected for comparison. A total of 15 overlapping genes were identified as core targets: TNF, AKT1, SRC, EGFR, PTGS2, ESR1, MMP9, STAT3, CTNNB1, BCL2, MAPK3, GSK3B, HSP90AA1, ICAM1, and MMP2.

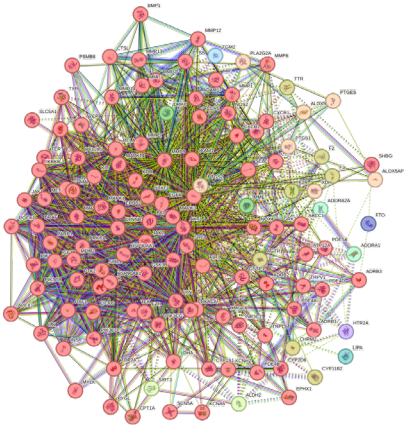

Figure 3: PPI Network

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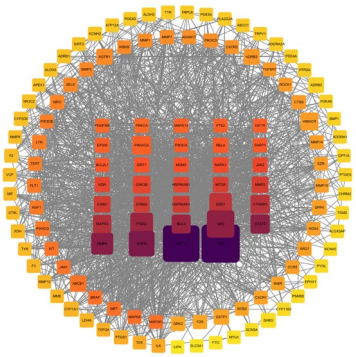

Figure 4: Degree Values of Predicted Targets

3.6 Results of GO Functional Enrichment Analysis and KEGG Pathway Enrichment Analysis

To elucidate the biological effects of Coptis chinensis on MF, 130 key targets were input into the Metascape system for GO enrichment analysis ($P < 0.05$), covering three dimensions: biological processes, molecular functions, and cellular components (Figure 5). Results revealed that these targets participated in 1,812 biological processes, 135 molecular functions, and 173 cellular components. The top 10 GO terms were identified and visualized. Biological processes included positive regulation of cell migration, cell motility, locomotion, cellular response to nitrogen compounds, and regulation of the MAPK cascade (Figure 5). Molecular functions encompassed phosphotransferase activity, with an alcohol group as acceptor, and kinase activity (Figure 5). Additionally, the relevant cellular components are primarily localized to the perinuclear region of the cytoplasm, membrane rafts, membrane microdomains, and focal adhesions. (Figure 5). To further elucidate how Coptis chinensis influences myocardial fibrosis through these potential targets, KEGG pathway enrichment analysis identified 198 enrichment pathways. The top 20 pathways ($P < 0.05$ and FDR < 0.05) primarily included Pathways in cancer, Prostate cancer, EGFR tyrosine kinase inhibitor resistance, Proteoglycans in cancer, PI3K-Akt signaling pathway, and other biological signaling pathways (Figure 5).

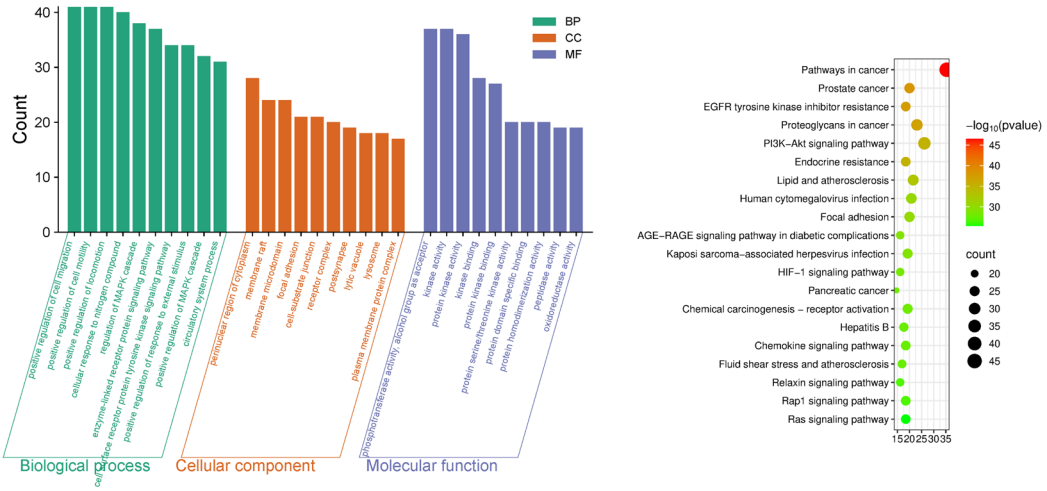

Figure 5: GO and KEGG Enrichment Analysis

4. Discussion

Research on myocardial fibrosis is rapidly expanding from traditional pathological mechanisms to frontier areas, including metabolism and the immune microenvironment. Traditional Chinese medicine (TCM), characterized by its "multicomponent, multitarget" properties, exhibits unique advantages in regulating these complex mechanisms. Its effects are not mediated through a single target; rather, they

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involve systematic intervention in the fibrosis network.

This study employed network pharmacology techniques to predict the active components, potential targets, and associated pathways of Coptis chinensis in treating myocardial fibrosis (MF). Analysis of traditional Chinese medicine (TCM) active component targets revealed chemical constituents highly correlated with Coptis chinensis, including berberine, obacunone, quercetin, and coptisine. The pathogenesis of myocardial fibrosis is multifactorial. It is widely recognized in the academic community that it is closely associated with multiple factors, including the core driving role of immune inflammation, the interplay between metabolic and epigenetic regulation, and imbalances in ion homeostasis[11][12][13]. Berberine exerts effects across multiple pathways of myocardial fibrosis. Regarding immune inflammation, it blocks NLRP3 inflammasome activation by inhibiting mTOR phosphorylation and reducing mitochondrial reactive oxygen species (mtROS) production, thereby lowering the levels of key pro-inflammatory factors IL-1β and IL-18 [14]. Obacunone stabilizes Nrf2 protein levels by inhibiting its ubiquitin-mediated degradation. This stabilization enhances the transcriptional activation of a battery of antioxidant genes, including HO-1 and NQO1. In experimental pulmonary fibrosis induced by bleomycin, this intervention effectively attenuated collagen deposition. Although direct studies of myocardial fibrosis are limited, given that oxidative stress represents a common pathological driver of fibrosis, this pathway likely exerts similar protective effects in the heart[15]. Quercetin exerts a central role by upregulating SIRT3. Its activation modulates mitochondrial metabolism and inhibits the TGF-β/Smad3 classical pro-fibrotic signaling pathway, thereby demonstrating anti-fibrotic effects in stress-loaded models and angiotensin II-stimulated fibroblasts[16]. Coptisine primarily targets the inhibition of the Rho/ROCK signaling pathway. This pathway plays a crucial role in regulating the cytoskeleton, inflammation, and apoptosis. Studies indicate that coptisine significantly reduces levels of inflammatory mediators (IL-1β, IL-6, TNF-α) and decreases myocardial cell apoptosis following myocardial ischemia/reperfusion injury by suppressing this pathway. Although direct evidence of its regulation on metabolism and ion homeostasis is limited, inhibiting Rho/ROCK itself helps improve abnormal mechanical stress signaling caused by cytoskeletal disruption, which may indirectly influence the fibrosis process[17].

Potential targets of Coptis chinensis active components (such as berberine) are significantly enriched in biological processes and cellular components that regulate cell migration, motility, MAPK cascades, kinase activity, as well as membrane microdomains and focal adhesions. Further KEGG pathway enrichment analysis revealed that these targets are highly concentrated in pathways such as the “PI3K - Akt signaling pathway,” “cancer pathways” (e.g., prostate cancer, EGFR tyrosine kinase inhibitor resistance), and “role of proteoglycans in cancer.” This is not a coincidence; rather, it profoundly reveals that myocardial fibrosis shares core molecular mechanisms with cancer-like proliferation, abnormal cell migration, and overactivation of survival signaling. The PI3K-Akt pathway is widely recognized as the master switch governing cellular survival and metabolic reprogramming. Activated Akt inhibits apoptosis by phosphorylating downstream targets such as mTOR and GSK-3β, while also directly promoting the synthesis of extracellular matrix (ECM) components like collagen[18]. The MAPK pathway, particularly p38 MAPK, directly responds to inflammatory and stress signals, regulating the expression of a series of pro-fibrotic genes such as TGF-β. The active components of Coptis chinensis are simultaneously enriched in both pathways, suggesting that they may suppress abnormal fibroblast activation and proliferation at multiple levels. This occurs by inhibiting one or more upstream targets (such as kinase activities involved in the enrichment results) while simultaneously blunting the transmission of PI3K - Akt and MAPK signaling axes. This mechanism strongly aligns with the compound's known pharmacological actions, including anti-inflammation and inhibition of excessive cell growth[19]. Coptis targets are enriched in focal adhesions and cell migration processes, strongly suggesting that its active components may inhibit fibroblast migration and infiltration into pathological areas by interfering with focal adhesion complex assembly or downstream signaling (such as cross-talk with the Rho/ROCK pathway), thereby limiting the spatial expansion of fibrosis. This provides a modern biological explanation for understanding Coptis' efficacy in “clearing heat and drying dampness” at the microscopic level of cellular dynamics[20]. The enrichment of Coptis chinensis' active components in these “cancer pathways” suggests that its anti-fibrotic action may resemble an “anti-cancer” strategy. This involves multi-target inhibition of these abnormally active proliferation and survival signaling networks, thereby promoting the reversion of activated fibroblasts to a normal state or increasing their sensitivity to apoptosis. This provides a novel and compelling theoretical perspective for developing natural compound-based anti-fibrotic therapies.

In summary, Coptis exerts its therapeutic effects in ameliorating myocardial fibrosis by acting on multiple targets and pathways via various active components. These findings offer significant theoretical support for the clinical application of Coptis in the treatment of myocardial fibrosis.

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