Active Ingredients and Targets of Guanxin No. 3 Formula in the Treatment of Myocardial Infarction: An Analysis Based on Network Pharmacology and Molecular Docking Techniques

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Abstract [**Objectives**] To investigate the active ingredients and targets of Guanxin No. 3 Formula in the treatment of myocardial infarction (MI) through the application of network pharmacology and molecular docking techniques. [**Methods**] The active ingredients and corresponding targets of Guanxin No. 3 Formula were identified using the TCMSP database, while MI targets were retrieved from the GeneCards and OMIM databases. Following the identification of overlapping targets, a "drug-active ingredient-target" network was constructed. A protein-protein interaction (PPI) network was subsequently established utilizing the STRING database. GO and KEGG enrichment analyses were performed via the DAVID platform. Molecular docking validation was conducted employing AutoDock Vina and PyMOL software. [**Results**] A total of 124 active ingredients were identified, corresponding to 190 MI-related targets. The key targets included IL6, AKT1, TP53, TNF, IL1B, *etc*. KEGG pathway enrichment analysis mainly involved lipid and atherosclerosis, and signaling pathways such as TNF, IL-17, HIF-1, and PI3K-Akt. Molecular docking results demonstrated that key ingredients, including luteolin, quercetin, and β-sitosterol, exhibited strong binding affinities with these key targets. [**Conclusions**] Guanxin No. 3 Formula may exert anti-MI effects by regulating inflammatory responses, inhibiting apoptosis, and promoting angiogenesis via multiple ingredients and targets.

Key words Guanxin No. 3 Formula, Network pharmacology, Myocardial infarction (MI), Molecular docking, Signal pathway

1 Introduction

Myocardial infarction (MI) is clinically characterized by the presence of abnormal cardiac biomarkers indicative of acute myocardial injury, accompanied by evidence of acute myocardial ischemia[1]. Patients presenting with acute MI typically exhibit persistent, severe retrosternal pain, fever, leukocytosis, elevated serum myocardial enzyme levels, and characteristic electrocardiographic changes consistent with acute myocardial injury, ischemia, and necrosis. These patients may develop arrhythmias, shock, or heart failure, representing severe manifestations of coronary heart disease[2]. The annual incidence rate of MI in China ranges from 0.2% to 0.6% and has exhibited an increasing trend in recent years. The incidence rate in the Beijing-Tianjin region is higher than that observed in southern China, while rates in Europe and America exceed those in China. Approximately 90% of MI cases are attributable to coronary atherosclerosis, with a minority resulting from syphilitic aortitis, coronary artery embolism, and coronary artery spasm. The male-to-female patient ratio is approximately between 2∶1 and 5∶1. Most patients are over 40 years of age, with the onset of MI in women occurring approximately 10 years later than in men[2]. Contemporary treatment approaches for MI primarily involve Western medicine, interventional therapies, cardiac assist devices, and heart transplantation. Although traditional Chinese medicine (TCM) does not occupy a predominant role in the current management of acute MI, sustained efforts by successive generations of medical experts, particularly through its integration with modern scientific and technological advancements, have enabled TCM to increasingly exhibit unique characteristics and advantages in the treatment of MI[3-4].

TCM therapy has increasingly become a significant approach in the clinical management of MI owing to its benefits in preventing restenosis following interventional procedures, mitigating no-reflow phenomena after reperfusion, alleviating patients' clinical symptoms, enhancing quality of life, improving exercise tolerance, and contributing to better long-term patient outcomes. According to TCM, MI is classified under conditions such as "chest obstruction", "heart pain", and "palpitations". The standardized prescription employed by Zhongshan Hospital of Traditional Chinese Medicine, known as Guanxin No. 3 Formula, is derived from the Gualou Xiebai Banxia Decoction described in Zhang Zhongjing's *Jinkui Yaolue* (*Synopsis of the Golden Chamber*). This formula primarily comprises Trichosanthis Pericarpium, Trichosanthis Semen, Allii Macrostemonis Bulbus, Rhizoma Pinelliae, Aurantii Fructus Immaturus, Salviae Miltiorrhizae Radix et Rhizoma, Amomi Fructus, and Santali Albi Lignum. It is traditionally believed to promote qi circulation, resolve phlegm, activate blood flow, and unblock meridians, and is principally used to treat chest obstruction and heart pain. This prescription is frequently employed in clinical practice for the treatment of MI, demonstrating clear therapeutic efficacy and receiving high patient acclaim. However, its underlying mechanism of action remains unreported. The present study aims to utilize network pharmacology and molecular docking techniques to construct a "drug-active ingredient-target-pathway" association network for the treatment of MI with

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Guanxin No. 3 Formula. Additionally, it seeks to predict the binding patterns between key ingredients and core targets, thereby elucidating the mechanism of action of Guanxin No. 3 Formula in treating MI from the holistic perspective of TCM.

2 Data sources and research methods

2.1 Chemical ingredient collection and target prediction of Guanxin No. 3 Formula Using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP; https://tcmsp-e.com/), active ingredients of Aurantii Fructus Immaturus, Allii Macrostemonis Bulbus, Rhizoma Pinelliae, Salviae Miltiorrhizae Radix et Rhizoma, Amomi Fructus, Santali Albi Lignum, and Fructus Trichosanthis were identified and screened under the conditions of oral bioavailability (OB) ≥30% and drug-likeness (DL) ≥0.18. The corresponding targets were then cross-referenced with UniProt (https://www.uniprot.org/), and non-human genes and duplicate entries were removed to obtain standardized gene names.

2.2 Acquisition of MI-related targets The key word "myocardial infarction" was used to retrieve disease-related targets from the GeneCards (https://www.genecards.org/) and OMIM (https://www.omim.org/) databases. All identified targets were compiled into an Excel sheet, duplicates were removed, and gene information was verified and standardized using the UniProt database.

2.3 Construction of drug-disease target prediction and network The drug ingredient targets were mapped onto the disease targets, and a Venn diagram was generated to identify the intersecting genes. The "drug-ingredient-target" network was constructed using Cytoscape 3.7.2 software.

2.4 Construction of target protein interaction network To further investigate the protein-protein interactions associated with Guanxin No. 3 Formula in the treatment of MI, the intersecting genes were uploaded to the STRING database (https://string-db.org/) to construct a protein-protein interaction (PPI) network. The species was specified as "*Homo sapiens*", the minimum interaction score was set to 0.7, and all other parameters were maintained at their default values. The resulting data were saved in TSV format and subsequently imported into Cytoscape 3.7.2 for network analysis (Cytoscape→Tools→Network Analyzer →Network Analysis → Analysis Network). Node size and color intensity corresponded to the degree value, with larger nodes indicating higher degree values. Edge thickness represented the combined score, where thicker edges indicated higher combined scores. Core targets were screened, and the PPI network diagram was constructed accordingly.

2.5 GO enrichment analysis and KEGG pathway analysis Genes intersecting between drugs and diseases were uploaded to the DAVID database (https://david.ncifcrf.gov/summary.jsp), with OFFICIAL_GENE_SYMBOL identifiers selected and the species specified as "*Homo sapiens*". GO functional analysis was performed using DAVID 6.8, annotating the target proteins' functions across three categories: biological process (BP), cellular component (CC), and molecular function (MF). KEGG pathway enrichment analysis was conducted. The top 10 terms from BP, CC, and MF categories in the GO analysis, along with 20 MI-related pathways identified in the KEGG analysis ($P<0.01$), were selected as the principal gene functional enrichment processes and signaling pathways associated with Guanxin No. 3 Formula in the treatment of MI, in order to elucidate the potential mechanisms underlying its therapeutic effects.

2.6 Molecular docking Generally, a higher degree value within the network indicates greater node importance. Specifically, proteins exhibiting higher degree values in the PPI network may play a critical role in the pharmacological treatment of MI. To validate the interaction activities between active ingredients and key targets, molecular docking was conducted using AutoDock Vina (1.1.2). The specific method was as follows: (i) compounds in mol2 format were downloaded from the TCMSP official website, imported into ChemBio3D for energy minimization, and subsequently imported into AutoDockTools 1.5.6 for hydrogen addition, charge calculation, charge assignment, and rotatable bond designation, after which they were saved in the "pdbqt" format. (ii) Key target proteins were obtained from the Protein Data Bank (PDB; http://www.rcsb.org/), prioritizing human proteins, original ligands exhibiting high structural similarity to the active ingredients, and structures with high resolution. (iii) Proteins were loaded into PyMOL (2.3.0) to remove original ligands and water molecules, then imported into AutoDockTools (1.5.6) for hydrogen addition, charge calculation, charge assignment, atomic type specification, and saved in the "pdbqt" format. (iv) Protein binding sites were predicted using POCASA 1.1, with the grid box size set to 60×60×60 and a grid spacing of 0.37 Å; all other parameters were maintained at default settings. (v) Interaction mode analysis was performed using PyMOL 2.3.0.

3 Results and analysis

3.1 Prediction of active ingredients and targets of Guanxin No. 3 Formula Using the TCMSP database and applying the criteria of OB≥30% and DL≥0.18, followed by the removal of invalid components, a total of the following active ingredients were identified and collected: 19 from Aurantii Fructus Immaturus, 11 from Allii Macrostemonis Bulbus, 12 from Rhizoma Pinelliae, 60 from Salviae Miltiorrhizae Radix et Rhizoma, 9 from Amomi Fructus, 3 from Santali Albi Lignum, and 10 from Fructus Trichosanthis.

3.2 MI-related targets and drug-disease intersecting targets A total of 5 557 and 39 targets were identified from the GeneCards and OMIM databases, respectively. Following the removal of duplicates, 5 580 MI-related targets were obtained and subsequently validated using the UniProt database. By intersecting the drug's action targets with the MI-related targets, 190 intersecting target genes were identified, representing potential therapeutic targets for the treatment of MI with Guanxin No. 3 Formula (Fig.1).

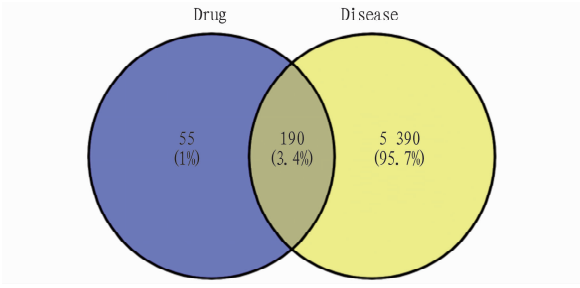
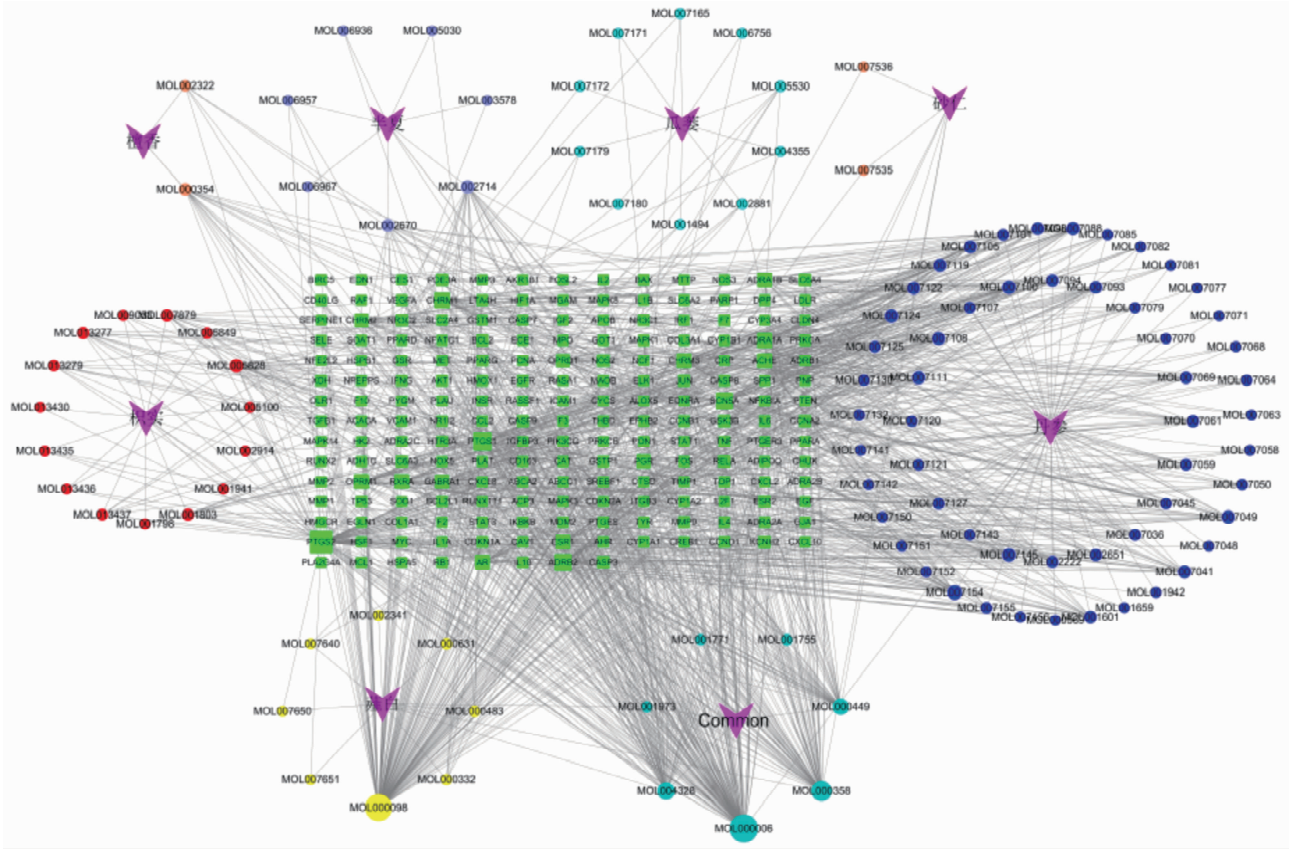


Fig. 1 Venn diagram of compounds and diseases

3.3 Prediction results of drug-ingredient-target The files "network. xlsx" and "type. xlsx", which were generated based on drug-ingredient-target data, were imported into Cytoscape 3.7.2 for visual analysis. The resulting network comprised 304 nodes and 1 260 edges. As illustrated in Fig. 2, the top five core ingredients ranked by degree value were luteolin (MOL000006), quercetin (MOL000098), β-sitosterol (MOL000358), naringenin (MOL004328), and stigmasterol (MOL000449).

3.4 Key targets and PPI network A total of 190 intersecting target genes were uploaded to the STRING database (https://string-db.org/) for PPI prediction. The species was specified as "*Homo sapiens*", and the confidence score threshold was set at 0.7. The resulting network file was saved in TSV format and subsequently imported into Cytoscape 3.7.2 to construct the PPI network. Targets with a degree value greater than 9 were selected, resulting in a network comprising 101 nodes and 2 596 edges. A topological analysis of the network was performed. Node size and color corresponded to the degree value, while edge thickness represented the combined score. The analysis identified IL6, AKT1, TP53, IL1B, TNF, STAT3, EGFR, JUN, CASP3, and MMP9 as core targets (Fig. 3).



NOTE Rectangles denote targets, ellipses signify drug ingredients, and rhombic nodes correspond to traditional Chinese medicine.

Fig. 2 Drug-ingredient-target network

3.5 Biological function enrichment analysis

3.5.1 GO enrichment analysis. GO functional enrichment analysis of the intersecting genes between the drug and disease was per-

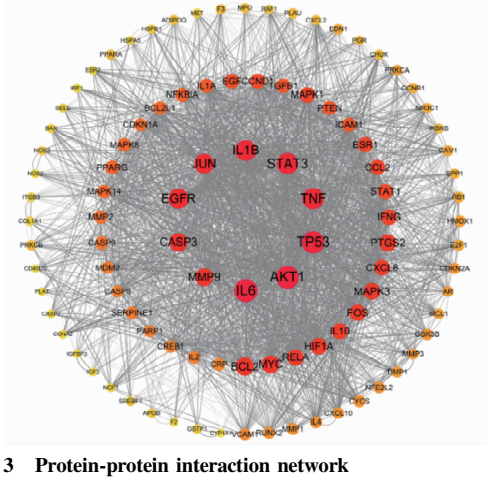


Fig. 3 Protein-protein interaction network

formed using the DAVID database. A total of 606 GO terms were identified. Applying a significance threshold of $P<0.01$, 464 BP terms significantly enriched in the treatment of MI with Guanxin No. 3 Formula were selected. These processes primarily included positive regulation of gene expression, signal transduction, response to xenobiotic stimulus, negative regulation of apoptosis, apoptosis, positive regulation of cell proliferation, inflammatory response, response to hypoxia, positive regulation of apoptosis, and G protein-coupled receptor signaling pathways. Additionally, 56 CC terms were identified, encompassing the nucleus, cytosol, plasma membrane, cytoplasm, nucleoplasm, extracellular space, extracellular region, membrane, integral component of plasma membrane, and extracellular exosomes. Furthermore, 86 MF terms were enriched, including protein binding, identical protein binding, enzyme binding, protein homodimerization activity, DNA binding, zinc ion binding, protein kinase binding, sequence-specific DNA binding, protein heterodimerization activity, and ubiquitin protein ligase binding, as illustrated in Fig. 4.

3.5.2 KEGG pathway enrichment analysis. Pathway enrichment analysis was performed using the DAVID database, resulting in the identification of 130 enriched pathways. Based on a significance threshold of $P<0.01$, 99 pathways were considered significantly enriched. Among these, pathways associated with MI included lipid and atherosclerosis, fluid shear stress and atherosclerosis, TNF signaling pathway, IL-17 signaling pathway, HIF-1 signaling pathway, endocrine resistance, PI3K-Akt signaling pathway, Th17 cell differentiation, FoxO signaling pathway, MAPK signaling pathway, T cell receptor signaling pathway, Toll-like receptor signaling pathway, p53 signaling pathway, NF-κB signaling pathway, VEGF signaling pathway, thyroid hormone signaling pathway, Th1 and Th2 cell differentiation, cGMP-PKG signaling pathway, ErbB signaling pathway, and NOD-like receptor signaling pathway, as illustrated in Fig. 5.

Based on the *P*-value, the top 20 KEGG metabolic pathways were identified, and a bubble chart was constructed. The horizontal axis represented the number of genes enriched in each pathway; the size of the bubbles corresponded to the number of genes, while the color intensity reflected the level of statistical significance. This visualization can effectively convey the information regarding significant enrichment.

3.6 Molecular docking results Based on the aforementioned analysis, the top five significant targets were selected for semi-flexible docking with compounds exhibiting higher degree values. The binding strength between small molecules and target proteins was quantified by affinity. A binding energy value less than zero indicates that the small molecule can spontaneously bind to the target protein, with lower values corresponding to a higher likelihood of binding.

The docking results demonstrated that all small molecules were capable of entering the active site of target proteins. The small molecules exhibiting the most favorable docking interactions with each target protein were selected for detailed analysis. Specifically, luteolin formed hydrogen bonds with ALA-230 of AKT1, with bond lengths of 2.4 and 2.2 Å, respectively. β-Sitosterol established a hydrogen bond with SER-84 of IL1B, with a bond length of 2.2 Å. Stigmasterol formed a hydrogen bond with ARG-179 of IL6, with a bond length of 2.0 Å. β-sitosterol formed hydrogen bonds with GLU-116 and ARG-98 of TNF, with bond lengths of 1.9 and 2.8 Å, respectively. Luteolin also formed hydrogen bonds with HIS-115, ASN-131, and SER-269 of TP53, with bond lengths of 2.5, 2.2, and 2.8 Å, respectively (Table 1, Fig. 6).

Table 1 Docking results of key small molecules with core target proteins

Target	PDB ID	Compound	Binding energy kcal/mol	Target	PDB ID	Compound	Binding energy kcal/mol
IL6	1ALU	MOL000006	−7.0	TNF	2E7A	MOL000006	−8.9
		MOL000098	−7.0			MOL000098	−9.0
		MOL000358	−6.7			MOL000358	−9.1
		MOL000449	−7.3			MOL000449	−8.9
		MOL004328	−6.5			MOL004328	−8.2
AKT1	6NPZ	MOL000006	−8.4	IL1B	6I8Y	MOL000006	−6.7
		MOL000098	−7.8			MOL000098	−6.3
		MOL000358	−7.7			MOL000358	−7.3
		MOL000449	−7.3			MOL000449	−6.8
		MOL004328	−7.2			MOL004328	−6.8
TP53	4GAP	MOL000006	−7.2				
		MOL000098	−6.4				
		MOL000358	−6.7				
		MOL000449	−6.8				
		MOL004328	−7.0				

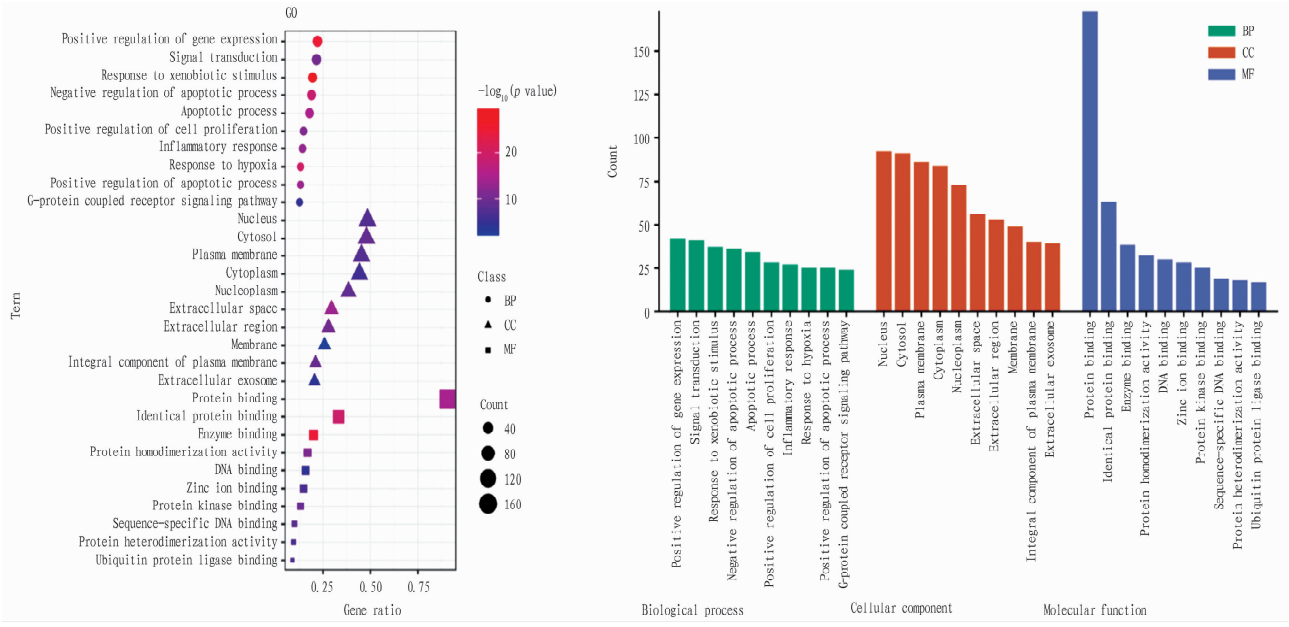
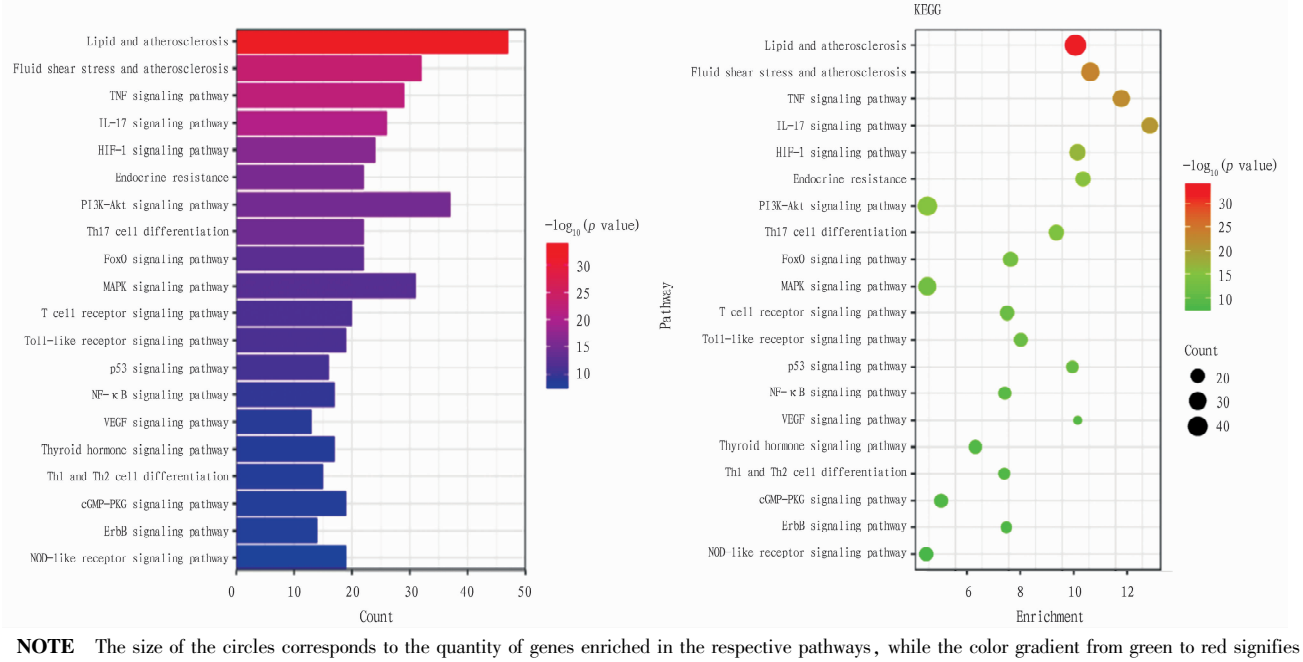
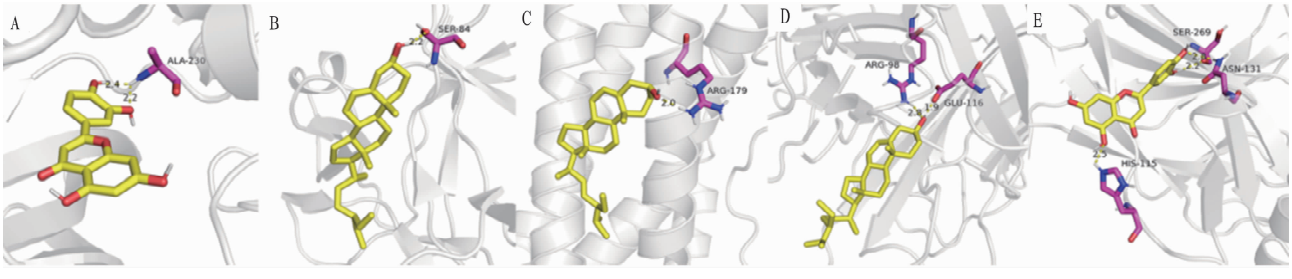


Fig. 4 Target GO function analysis of Guanxin No. 3 Formula in the treatment of myocardial infarction



NOTE The size of the circles corresponds to the quantity of genes enriched in the respective pathways, while the color gradient from green to red signifies a decreasing *P*-value.

Fig. 5 KEGG enrichment analysis of intersecting targets



NOTE A. Luteolin and AKT1; B. Beta-sitosterol and IL1B; C. Stigmasterol and IL6; D. Bet-sitosterol and TNF; E. Luteolin and TP53.

Fig. 6 Protein-protein interaction patterns

4 Discussion

MI is an acute necrotizing condition that arises from coronary atherosclerosis, wherein plaque rupture induces secondary thrombosis, resulting in sustained ischemia and hypoxia of the myocardium. The pathological process encompasses multiple interconnected mechanisms, including oxidative stress, inflammatory responses, apoptosis, and subsequent fibrotic remodeling and angiogenesis, which are temporally sequential and spatially interactive[5-6]. In TCM, MI is categorized under "chest obstruction" and "heart pain", with its pathogenesis attributed to a fundamental deficiency accompanied by excessive symptoms, the coexistence of phlegm and blood stasis, and obstruction of the heart meridian. Guanxin No. 3 Formula is designed to promote the circulation of qi, resolve phlegm, activate blood circulation, and unblock meridians, aligning with the pathological characteristics of MI, which involve "phlegm and blood stasis obstructing the meridians". This study systematically investigated the mechanism of action of Guanxin No. 3 Formula in treating MI through network pharmacology prediction and molecular docking validation. The findings indicate that the formula, whose principal active ingredients include luteolin, quercetin, β-sitosterol, naringenin, stigmasterol, and other flavonoids and phytosterols, may exert a comprehensive myocardial protective effect by modulating three key pathological processes: inflammatory response, cell survival and apoptosis, and matrix remodeling and angiogenesis.

4.1 Anti-inflammatory effects and regulation of atherosclerosis Atherosclerosis is the primary pathological foundation of MI. The processes of lipid deposition, endothelial dysfunction, and chronic inflammation collectively contribute to the formation and rupture of atherosclerotic plaques[7]. Following the onset of MI, necrotic myocardial tissue releases damage-associated molecular patterns, which activate the innate immune response. Subsequently, neutrophils and monocytes/macrophages infiltrate the infarcted region, secreting pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β. These factors exacerbate myocardial injury and ventricular remodeling while facilitating the clearance of necrotic tissue[8-10]. Inflammation and thrombosis exhibit a reciprocal relationship[11], and both the magnitude and resolution timing of the immune response critically influence the efficacy of post-infarction repair[12]. In this study, inflammation-related molecules, including IL6, TNF, IL1B, STAT3, and JUN, accounted for a high proportion of the core targets and were significantly enriched in signaling pathways such as NF-κB, TNF, IL-17, and Toll-like receptor[13-14]. These molecules are involved in pathological processes associated with metabolism and inflammation, alongside pathways related to lipid metabolism and atherosclerosis, as well as fluid shear stress and atherosclerosis. The ingredients of the formula, such as Fructus Trichosanthis, Allii Macrostemonis Bulbus, and Rhizoma Pinelliae, are traditionally used to clear phlegm and disperse nodules, whereas Salviae Miltiorrhizae Radix et Rhizoma promotes blood circulation and resolves blood stasis. This aligns with the pathogenesis of MI, which is characterized by "the coexistence of phlegm and blood stasis". Previous studies have demonstrated that luteolin can inhibit NF-κB and MAPK signaling pathways, thereby reducing levels of inflammatory factors such as TNF-α, IL-6, and IL-1β[15]. Quercetin has been shown to improve vascular endothelial dysfunction[16], and β-sitosterol exhibits lipid metabolism regulation and anti-inflammatory effects[17]. These findings corroborate the predictive results obtained in the present study.

4.2 Inhibiting myocardial cell apoptosis and promoting cell survival Myocardial cell apoptosis is a critical factor contributing to the expansion of the infarcted area and the subsequent deterioration of cardiac function following MI[18]. In this study, AKT1, TP53, and CASP3 were identified as key regulatory nodes involved in cardiomyocyte survival and apoptosis. AKT1 serves as a central component of the PI3K/AKT signaling pathway, which promotes cell survival and inhibits apoptosis, thereby playing a vital role in myocardial protection[19]. TP53 and CASP3 are participated in the initiation and execution phases of apoptotic signaling[18]. GO enrichment analysis further revealed that the target genes were predominantly associated with processes such as the negative regulation of apoptosis and the positive regulation of cell proliferation. Based on these findings, it is hypothesized that Guanxin No. 3 Formula may mitigate myocardial cell apoptosis by activating the PI3K-Akt signaling pathway and inhibiting p53 signaling pathway and apoptotic pathways, ultimately reducing the extent of myocardial injury.

4.3 Promoting angiogenesis and regulating fibrotic remodeling The prognosis during the MI repair phase is closely associated with the balance between angiogenesis and fibrotic remodeling. In this study, significant enrichment was observed in both the HIF-1 signaling pathway, a critical mechanism for hypoxia adaptation[20], and the VEGF signaling pathway, which facilitates the establishment of peripheral circulation and angiogenesis within ischemic regions[21]. Phenotypic alterations such as endothelial-to-mesenchymal transition in endothelial cells post-infarction were participated in the processes of angiogenesis and fibrosis[22]. These findings suggest that Guanxin No. 3 Formula may enhance blood supply to ischemic myocardium by improving hypoxia adaptation and promoting angiogenesis. Targets including MMP9 and EGFR are involved in extracellular matrix degradation and fibroblast activation, thereby influencing scar formation and ventricular remodeling following infarction[23-24]. Considering the GO enrichment results, particularly those related to the "response to hypoxia", it can be inferred that the therapeutic effects of Guanxin No. 3 Formula involve multiple stages in the pathogenesis and progression of MI, rather than being confined to a single target or

pathway.

4.4 Molecular docking verification and comparison with analogous studies The molecular docking results corroborate the aforementioned predictions from a spatial conformation perspective. Specifically, luteolin forms hydrogen bonds with AKT1 (ALA-230) and TP53 (HIS-115, ASN-131, SER-269); β-sitosterol interacts with IL1B (SER-84) and TNF (GLU-116, ARG-98); and stigmasterol binds to IL6 (ARG-179). All binding energies were negative, indicating that these core ingredients can stably associate with target proteins involved in inflammation, survival, and apoptosis. These findings provide structural-level evidence supporting the results obtained from network pharmacology analysis.

Compared to analogous studies, the findings of this research exhibit both similarities and distinct characteristics. Network pharmacological investigations into the treatment of MI using compound prescriptions such as Shenfu Decoction[4] and Ganjiang Fuzi Decoction[25] employed comparable analytical approaches. Their core targets predominantly involved molecules associated with inflammation and cell survival, including IL-6, TNF, and AKT1. These results suggest the existence of a common mechanistic basis underlying the treatment of MI with various TCM compound prescriptions, primarily through the regulation of inflammation and cell survival pathways. Furthermore, these findings support the reliability of network pharmacology methods in elucidating the mechanisms of compound prescriptions[26]. Guanxin No. 3 Formula is developed on the interrelationship between phlegm and blood stasis, with its composition primarily aimed at resolving phlegm and promoting blood circulation. Pathway enrichment analysis reveals a predominant focus on hypoxia adaptation and angiogenesis-related signaling pathways, including HIF-1 and VEGF, as well as the PI3K-Akt survival signaling pathway. Shenfu Decoction primarily functions to warm yang and benefit qi, whereas Ganjiang Fuzi Decoction is oriented towards restoring yang and alleviating adverse reactions. The distinct characteristics of the target pathways associated with these prescriptions differ from those of Guanxin No. 3 Formula. These differences reflect the underlying pathogenesis and the unique therapeutic principles of each prescription, thereby providing a molecular-level basis for "correlating specific prescriptions with corresponding syndromes" to a certain extent.

5 Conclusions and prospects

This study initially clarified the potential molecular mechanisms underlying the therapeutic effects of Guanxin No. 3 Formula in the treatment of MI, thereby providing reference targets and pathway information to support its clinical application and future research. Notably, compounds such as luteolin and quercetin, along with targets including IL-6, AKT1, and HIF-1/VEGF, warrant further experimental validation. However, several limitations should be acknowledged: both network pharmacology and molecular docking approaches rely on database information and computational predictions, necessitating confirmation through *in vivo* and *in vitro* experiments. Additionally, the databases utilized, such as TCMSP, contain limited information, and the use of OB and DL as screening criteria may have excluded some active ingredients Future studies employing MI animal models and cellular experiments will focus on validating the involvement of inflammatory, apoptotic, and angiogenic pathways to further elucidate the mechanisms by which Guanxin No. 3 Formula exerts its therapeutic effects in MI.

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