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Exploring the mechanism of Simiao Yong'an decoction in treating diabetic foot based on metabolomics

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ABSTRACT

Background: In recent years, diabetic foot has become a significant cause of disability and mortality among individuals with diabetes. With the progression of time and technology, both modern medicine and traditional Chinese medicine have gradually deepened their understanding and research into diabetic foot, further enhancing the treatment methods available for this condition. To a certain extent, this can alleviate patients' pain and improve their quality of life.
Objective: To explore the mechanism of Simiao Yong'an Decoction (SYD) in the treatment of diabetic foot (DF).
Methods: Databases and software such as TCMSP, GeneCards, OMIM, and TTD were used to identify the pharmacodynamic material basis, therapeutic targets, and metabolic pathways of SYD in the treatment of DF. The serum metabolomics of SYD was integrated with network pharmacology to validate the potential active components and metabolic pathways involved in SYD's intervention in DF.
Results: The main active components of SYD in treating DF were found to be luteolin, quercetin, and formononetin. The treatment may act through targets such as AKT1, TNF, HSP90AA1, MAPK8, and STAT3, regulating pathways including the MAPK signaling pathway, TNF signaling pathway, phosphatidylinositol signaling pathway, HIF-1 signaling pathway, and Toll-like receptor signaling pathway. The phosphatidylinositol signaling pathway was consistent with the findings from serum metabolomics analysis of SYD.
Conclusion: The phosphatidylinositol signaling pathway may be a key metabolic pathway in the intervention of DF by SYD.

Introduction

Diabetic foot (DF) is a disease caused by lower limb venous damage and neuropathy due to diabetes, leading to lower limb infections, ulcers, and even deep tissue damage, which significantly reduces patients' quality of life.[1–3] Simiao Yong'an Decoction (SYD) consists of Lonicera japonica, Scrophularia ningpoensis, Angelica sinensis, and Glycyrrhiza. It is a classical prescription used in clinical treatment for carbuncles and abscesses, possessing heat-clearing, dampness-resolving, blood-activating, and stasis-removing properties. According to *Shen Yi Mi Chuan* by Hua Tuo, "intense heat toxicity" corresponds to "carbuncles" and "yin damage". DF ulcers fall within the categories of "gangrene", "xiaoke", and "sores" in Traditional Chinese Medicine (TCM), characterized by deficiency in origin and excess in manifestation, primarily due to blood stasis.[4] The underlying pathogenesis involves heat toxin accumulation, fluid exhaustion due to heat, and blood stasis, with treatment principles focusing on clearing heat, detoxifying, and promoting blood circulation to relieve pain. Previous studies on SYD have demonstrated its anti-inflammatory, anticoagulant, and anti-atherosclerotic effects, confirming its therapeutic efficacy.[5,6] To further investigate the mechanism of SYD in treating DF, this study integrates serum metabolomics with network pharmacology to identify the pharmacodynamic material basis and mechanism of action, laying the foundation for TCM treatment of DF.

Materials and methods

Databases and experimental instruments

The databases, platforms, and software used in this study are listed in Table 1. The main instruments used are as follows: Waters

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Table 1
Databases, platforms and software used in the study.

Database/Software	URL	Version
TCMSP Database[7]	https://tcmspw.com/tcmsp.php	2.3
Uniprot Database[8]	https://www.uniprot.org	
GeneCards Database[9]	http://www.genecards.org/	
OMIM Database[10]	https://omim.org	
TTD Database[11]	http://db.idrblab.net/ttd/	
String Database[12]	https://string-db.org	11b
Metascape Database[13]	https://metascape.org	
PDB Database[14]	https://www.rcsb.org	
Cytoscape[15]		3.8.0
AutoDockTools		1.5.6
Pymol		
RStudio		
Discovery Studio		4.5

ACQUITY ultra-performance liquid chromatography (UPLC) system (Waters Corporation, USA); Waters Premier LCT XE mass spectrometry system (Waters Corporation, USA); Masslynx 4.1 software workstation; Sorvall ST 16 R centrifuge (Thermo Scientific, USA); KQ-500DB ultrasonic cleaner (Kunshan Ultrasonic Instrument Co., Ltd.); Nichipet EX micro-pipettes (10–100 μL, 100–1000 μL, NICHIRYO, Japan); VX-II multi-tube vortex mixer (Beijing Tajin Technology Co., Ltd.); Thermo Scientific 995 ultra-low temperature freezer (Thermo Scientific, USA).

Reagents and subjects

Leucine enkephalin (LE) calibration solution and sodium formate calibration solution were purchased from Sigma. Chromatographic acetonitrile was purchased from Thermo Scientific. Ultrapure water was from Watsons Food & Beverage Co., Ltd. (Guangzhou, China). Chromatographic methanol and chromatographic formic acid were purchased from Dikma (USA). Other reagents were of analytical grade.

DF patients were recruited from the Burn Department, Vascular Surgery Department, and Nangang District Vascular Surgery Ward of Heilongjiang Provincial Hospital. A total of 60 patients with heat toxin exuberance type DF meeting the criteria were included and randomly divided into debridement, Western medicine, TCM, and combined treatment groups. Additionally, 15 healthy individuals were included as a control group.

Analysis of pharmacodynamic material basis and targets of SYD

The TCMSP database was searched using keywords: Lonicera japonica, Scrophularia ningpoensis, Angelica sinensis, and Glycyrrhiza. The retrieved components were screened based on oral bioavailability (OB) ≥ 30 % and drug-likeness (DL) ≥ 18 %, supplemented with literature reports.[3] The filtered components were then input into the TCMSP database to predict targets, and the corresponding target protein names were obtained from the Uniprot database. Gene names were converted using the Uniprot database, and the active components of SYD for diabetes treatment were identified. The GeneCards, OMIM, and TTD databases were searched for "diabetic foot", and candidate targets were screened based on reviewed and human sources. The GeneCards database targets were further filtered using the MEDIAN function based on relevance scores until the number of targets was reduced to below 2000. The final targets were integrated, and duplicates were removed to obtain disease-related targets.

Protein-protein interaction (PPI) network construction and core target screening

The intersection of TCM and disease-related targets was obtained using the VLOOKUP function and imported into the String platform. With a minimum interaction score of 0.9 and the organism set to "Homo sapiens", disconnected nodes were hidden, and the tsv file String1.tsv was output. The file was processed and filtered to obtain potential targets of SYD for DF. The tsv file was imported into Cytoscape 3.8.0, and the "cytoHubba" plugin was used to calculate and select the top 20 potential targets with high degree values.

TCM-pharmacodynamic material-target network and core component screening

The active components associated with potential targets were integrated with TCM potential targets and imported into Cytoscape 3.8.0 to generate a "TCM- pharmacodynamic material-potential target" network. The "Analyze Network" function was used to calculate and export a csv file, and the top 10 active components with the highest values were selected as core components.

GO and KEGG Pathway Enrichment Analysis

The potential targets were imported into the Metascape platform, and "custom analysis" was selected with default values of "Min Overlap" = 3, "P Value Cutoff" = 0.01, and "Min Enrichment" = 1.5. GO Molecular Functions (GO-MF), GO Biological Processes (GO-BP), GO Cellular Components (GO-CC), and KEGG Pathway enrichment were performed. The results were processed and visualized using RStudio.[3]

Molecular Docking

The PDB format files of core target proteins were downloaded from the PDB database, and mol2 format files were downloaded from TCMSP. AutoDockTools-1.5.6 was used for ligands removement, dehydration, and dehydrogenation, and charging were performed before saving in pdbqt format. Molecular docking was performed using AutoDock Vina, and results were visualized using PyMOL.

Chromatographic conditions and mass spectrometric analysis

A Waters ACQUITY UPLC BEH C18 column (1.8 μm, 2.1 × 100 mm) was used. The mobile phase consisted of (A) chromatographic acetonitrile (containing 0.1 % formic acid) and (B) ultrapure water (containing 0.1 % formic acid). The column temperature was set at 40°C, the sample chamber temperature at 4°C, and the flow rate at 0.4 ml/min. The injection volume was 5 μl, and the gradient elution conditions are shown in Table 2.

A Waters Premier LCT XE mass spectrometry system (high-resolution time-of-flight mass spectrometer) with an electrospray ionization (ESI) source was used. Nitrogen was used as the desolvation and protection gas, and data were acquired in negative ion mode. Data acquisition and processing were performed using Masslynx 4.1, Progenesis QI 2.3, and EZinfo 3.0 software. Capillary voltage: 1500 V; cone voltage: 60 V; ion source temperature: 110°C; desolvation temperature: 360°C; desolvation gas flow rate: 750 L/h; cone gas flow rate: 20 L/h. Full scans were performed in the m/z range of 100–1500 amu in negative ion mode, with real-time calibration using LE at a concentration of 1 ng/ml and a flow rate of 0.04 ml/min.

Table 2
Serum Metabolomics Gradient Elution Conditions.

Time (min)	Flow Rate (ml/min)	%A (0.1 %FA -ACN)	%B (0.1 %FA -H2O)
Initial	0.400	1.0	99.0
0.50	0.400	20.0	80.0
2.50	0.400	60.0	40.0
4.00	0.400	66.0	34.0
5.00	0.400	80.0	20.0
7.50	0.400	86.0	14.0
8.00	0.400	99.0	1.0
9.00	0.400	99.0	1.0

Serum sample processing and metabolic profile analysis

Serum samples were thawed at 4°C, and 200 μl of each sample was mixed with 3 volumes of −20°C pre-cooled methanol. The mixture was vortexed for 30 seconds, left at room temperature for 10 minutes to precipitate proteins, and centrifuged at 14,000 rpm for 20 minutes. The supernatant was collected and stored in vials for analysis.

Serum and urine samples were processed according to the above sample preparation method, and the established analytical method was used to perform full scans in negative ion mode, obtaining metabolic profile information for each subject. The mass spectrometry data were imported into Waters Progenesis QI 2.3 software for peak extraction, peak alignment, deconvolution, and normalization. The three-dimensional data of ion retention time, mass-to-charge ratio and peak intensity of metabolites were extracted, the extracted peak data were imported into Waters Ezifo 3.0 software for principal component analysis (PCA), and PCA score plots of the metabolic profiles of each group were generated.

Identification of biomarkers for the treatment of DF by SYD

LC-MS data were loaded into Progenesis QI software, and raw data were visualized at each analysis step. Ion intensity maps showing retention time, *m/z*, and feature intensity, as well as 2D maps of mass spectra and chromatograms, provided quality assurance for automatic calibration, peak matching, and compound deconvolution. Data were filtered using ANOVA P-value < 0.05 and VIP value > 1 as selection criteria, and then imported into EZinfo for analysis. Unsupervised principal component analysis (PCA) was used to check for outliers and classification trends, and data were

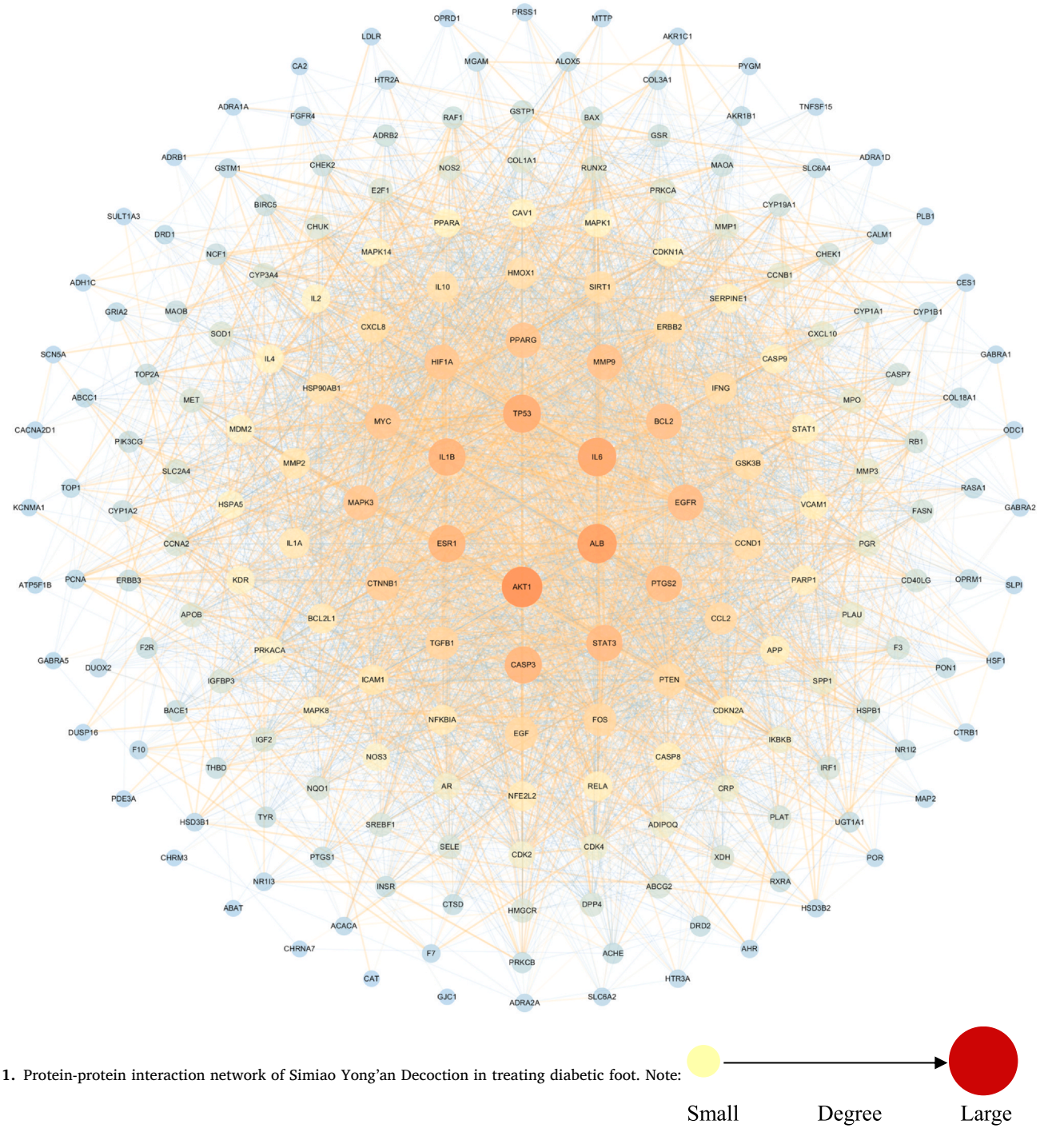

Fig. 1. Protein-protein interaction network of Simiao Yong'an Decoction in treating diabetic foot. Note:

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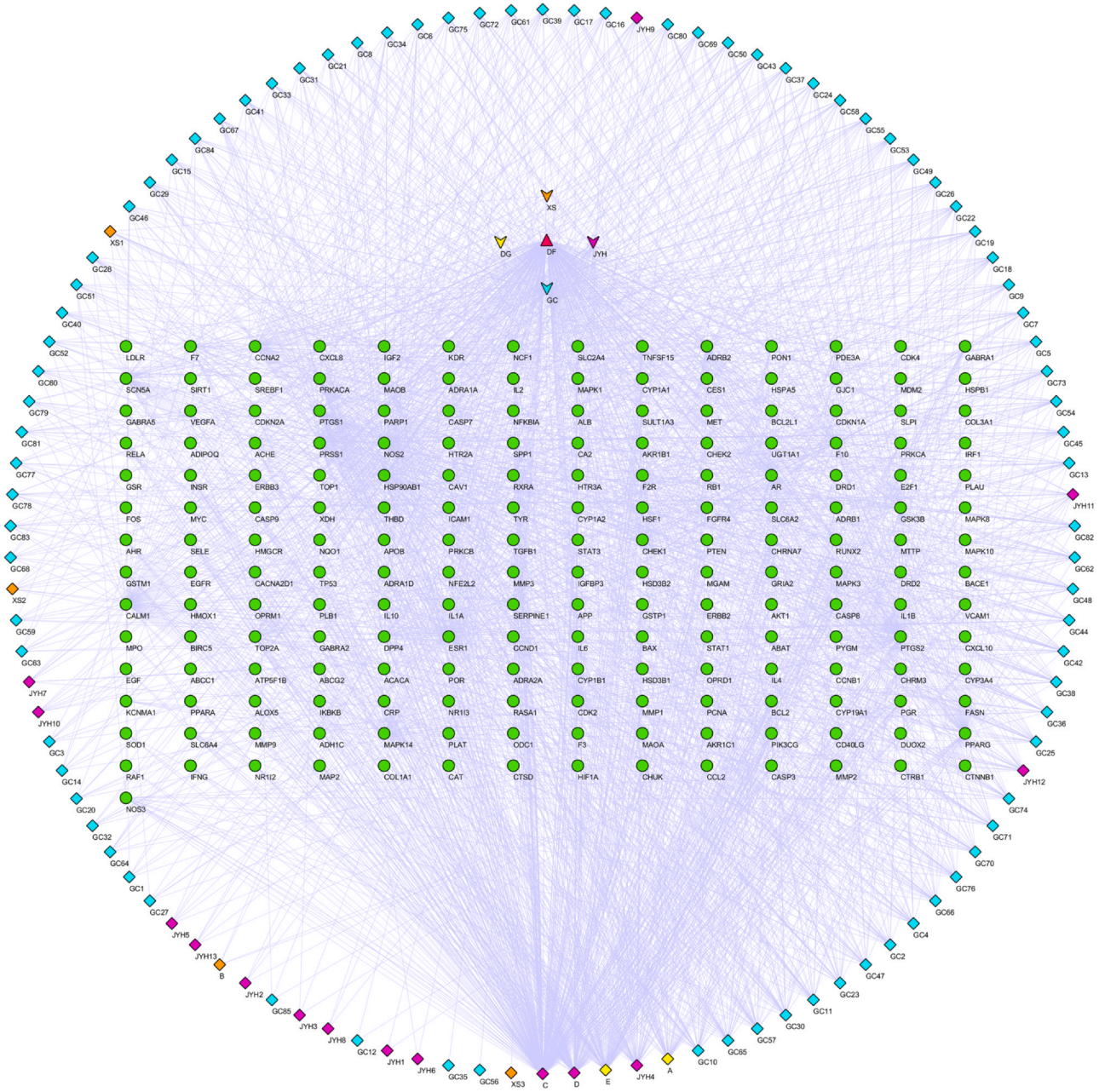

Fig. 2. TCM-pharmacodynamic material-target network. Note: Circular nodes represent potential targets, diamond-shaped nodes represent traditional Chinese medicines (TCMs), and hexagonal nodes represent active components. Blue represents targets, cyan represents Scrophularia ningpoensis, yellow represents Lonicera japonica, purple represents Angelica sinensis, brown represents Glycyrrhiza, and red represents shared components.

visualized. OPLS-DA was used to evaluate group differences. In the S-plot, each point represents an accurate mass retention time, with the X-axis representing variables. Points farther from the origin have higher relative contributions, and points at the ends of the S-plot represent ions with the highest confidence between groups.

Identification and metabolic pathway analysis of differential metabolites in SYD Treatment of DF

The retention time and *m/z* information of the differential metabolites in DF were imported into the metabolite identification module generated by Progenesis QI 2.3 software and labeled. Using the HMDB metabolite library, theoretical fragments were calculated with a mass deviation of 2 mDa and matched with the IDA data collected by mass spectrometry. The possible structures provided by the software were labeled and verified using the HMDB (http://www.hmdb.ca/), KEGG (http://www.genome.jp/kegg/), Massbank (http://www.massbank.jp/), and Metlin (http://metlin.scripps.edu) databases, combined with MS/MS data, to determine their structures.

The English names and KEGG or HMDB numbers of the differential metabolites were imported into the Metaboanalyst website (http://www.metaboanalyst.ca/) for pathway analysis. Metabolic pathways with significant contributions were identified, and corresponding metabolic pathway diagrams were drawn.

Results

Pharmacodynamic material basis and targets of SYD

The pharmacodynamic material basis and targets of the four herbs in SYD were obtained. Lonicera japonica had 19 active components,

Fig. 3. Gene ontology and KEGG pathway enrichment analysis. Note: (A) GO Molecular Function (GO-MF); (B) GO Biological Process (GO-BP); (C) GO Cellular Component (GO-CC); (D) KEGG pathway.

Scrophularia ningpoensis had 7, Angelica sinensis had 5, and Glycyrrhiza had 90. After merging and removing duplicates, a total of 115 active components were identified.

Using the Uniprot database, targets for DF were screened from the GeneCards, OMIM, and TTD databases. A total of 4682 targets were obtained from GeneCards, 95 from OMIM, and 11 from TTD. The GeneCards targets were further filtered using a relevance score ≥ 6.497622013, resulting in 1172 targets. After merging with OMIM and TTD targets and removing duplicates, 1203 disease-related targets were obtained.

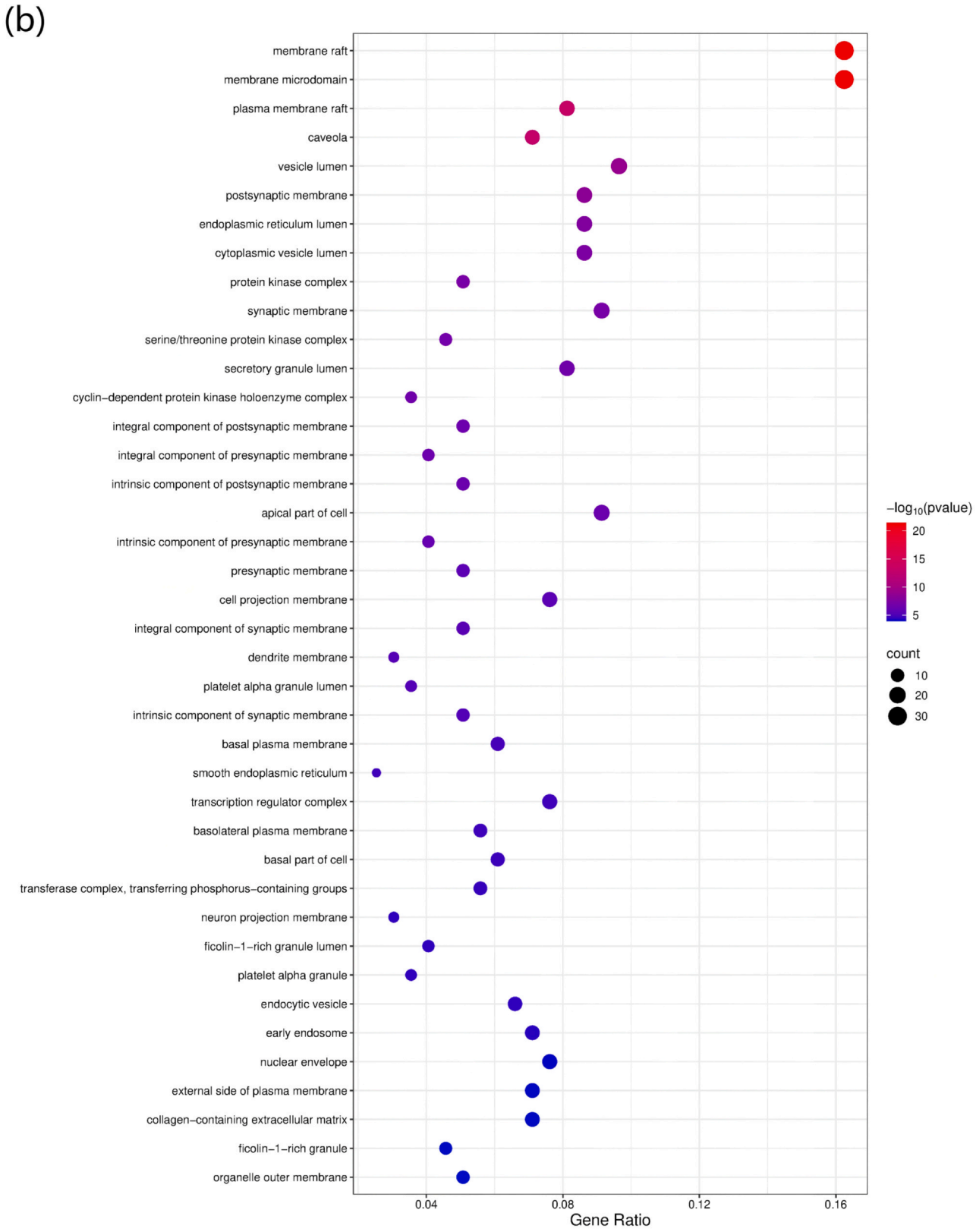

Fig. 3. (*continued*)

The intersection of TCM and disease-related targets yielded 136 targets, which were imported into the String platform for screening, resulting in 126 potential targets for SYD treatment of DF. The PPI network was visualized using Cytoscape 3.8.0, showing 126 nodes and 672 edges. The top 20 potential targets with the highest degree values were identified using the "cytoHubba" plugin: STAT3, AKT1, JUN, MAPK3, MAPK1, TNF, RELA, TP53, IL6, HSP90AA1, MAPK8, VEGFA, MAPK14, EGFR, APP, FOS, MYC, CXCL8, ESR1, and EGF (Fig. 1).

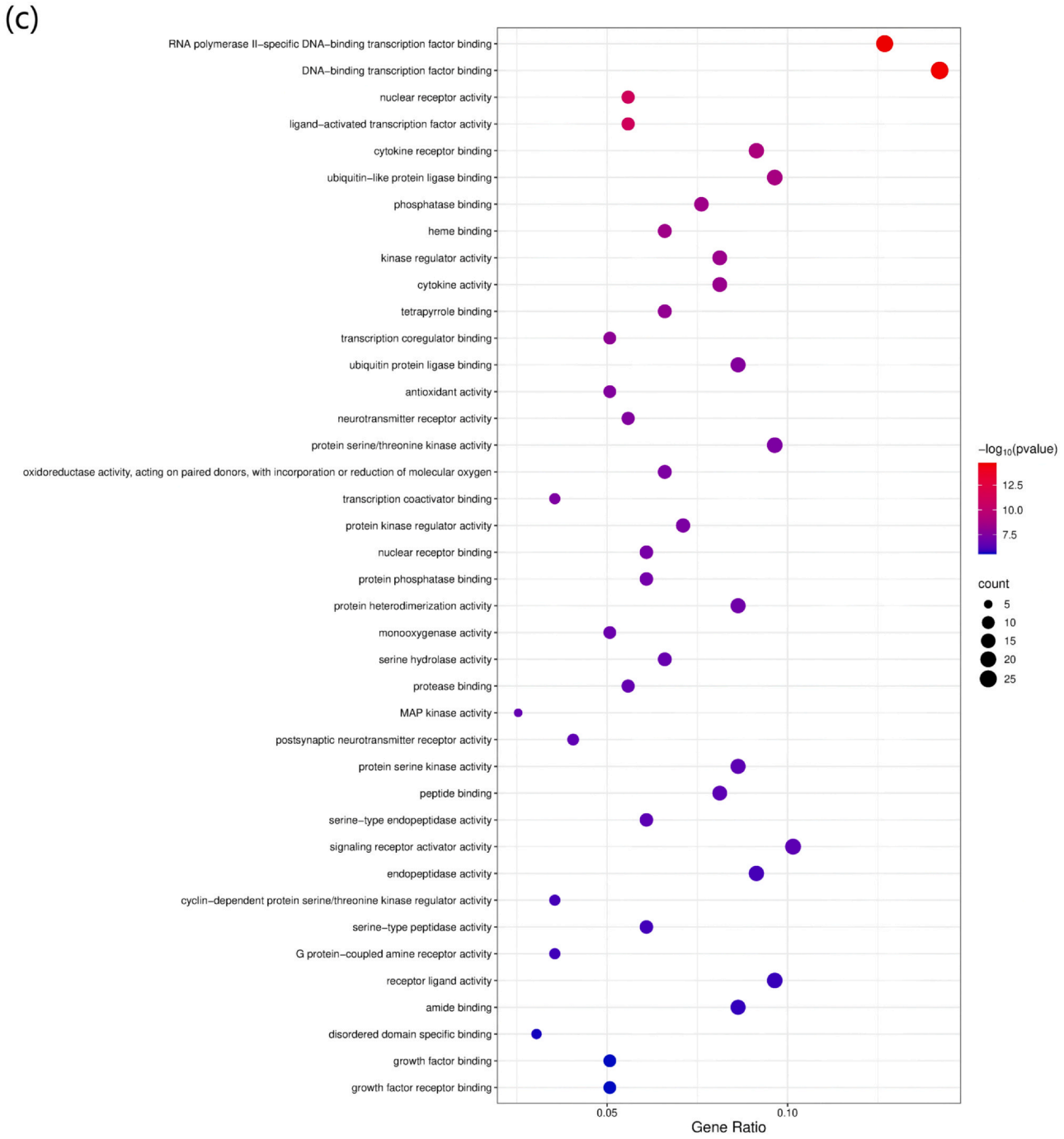

Fig. 3. (*continued*)

TCM- pharmacodynamic material -target network and core component screening

The network analysis in Cytoscape 3.8.0 revealed 237 nodes, including 4 TCM herbs, 107 active components, and 126 potential targets, with 1211 edges. The top 10 active components with the highest values were identified: MOL000006 (luteolin), MOL000098 (quercetin), MOL000358 (β-sitosterol), MOL000392 (formononetin), MOL000422 (kaempferol), MOL001789 (isoliquiritigenin), MOL003896 (7-methoxy-2-methylisoflavone), MOL004328 (naringenin), MOL002773 (β-carotene), and MOL000497 (licochalcone A) (Fig. 2).

GO and KEGG pathway enrichment analysis

Metascape software was used for GO and KEGG enrichment analysis of potential targets. A total of 143 GO terms, 2401 KEGG pathways, 115 GO-MF terms, and 209 GO-CC terms were obtained. The top 40 terms with the smallest LogP values were selected and visualized using bubble diagram (Fig. 3). GO-MF enrichment suggested that SYD has anti-DF effects. GO-CC enrichment indicated that SYD's anti-DF mechanism may be related to membrane rafts, membrane regions, vesicles, and cytoplasmic vesicles. KEGG pathway enrichment showed that SYD's therapeutic effects on DF may involve the AGE-RAGE signaling

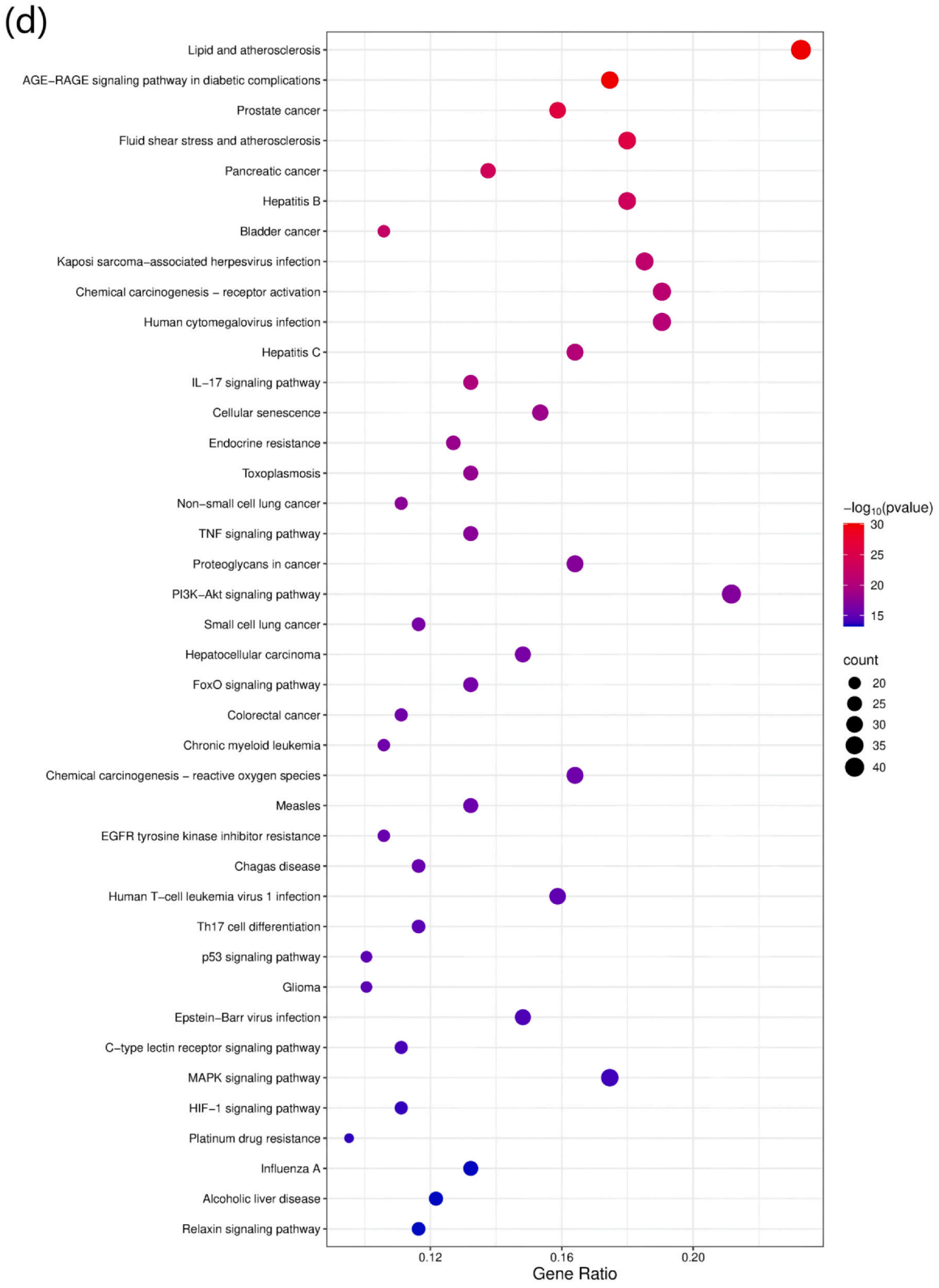

Fig. 3. (*continued*)

pathway in diabetic complications, fluid shear stress and atherosclerosis, phosphatidylinositol metabolism, IL-17 signaling pathway, MAPK signaling pathway, TNF signaling pathway, PI3K-Akt signaling pathway, HIF-1 signaling pathway, Th17 cell differentiation, apoptosis, T cell receptor signaling pathway, Toll-like receptor signaling pathway, and FoxO signaling pathway.

Molecular docking

Molecular docking was performed between core components and core targets, resulting in 60 docking results. Except for RELA, all core targets showed good binding activity with core components, with an average binding energy of −7.06 kcal/mol, confirming the feasibility of

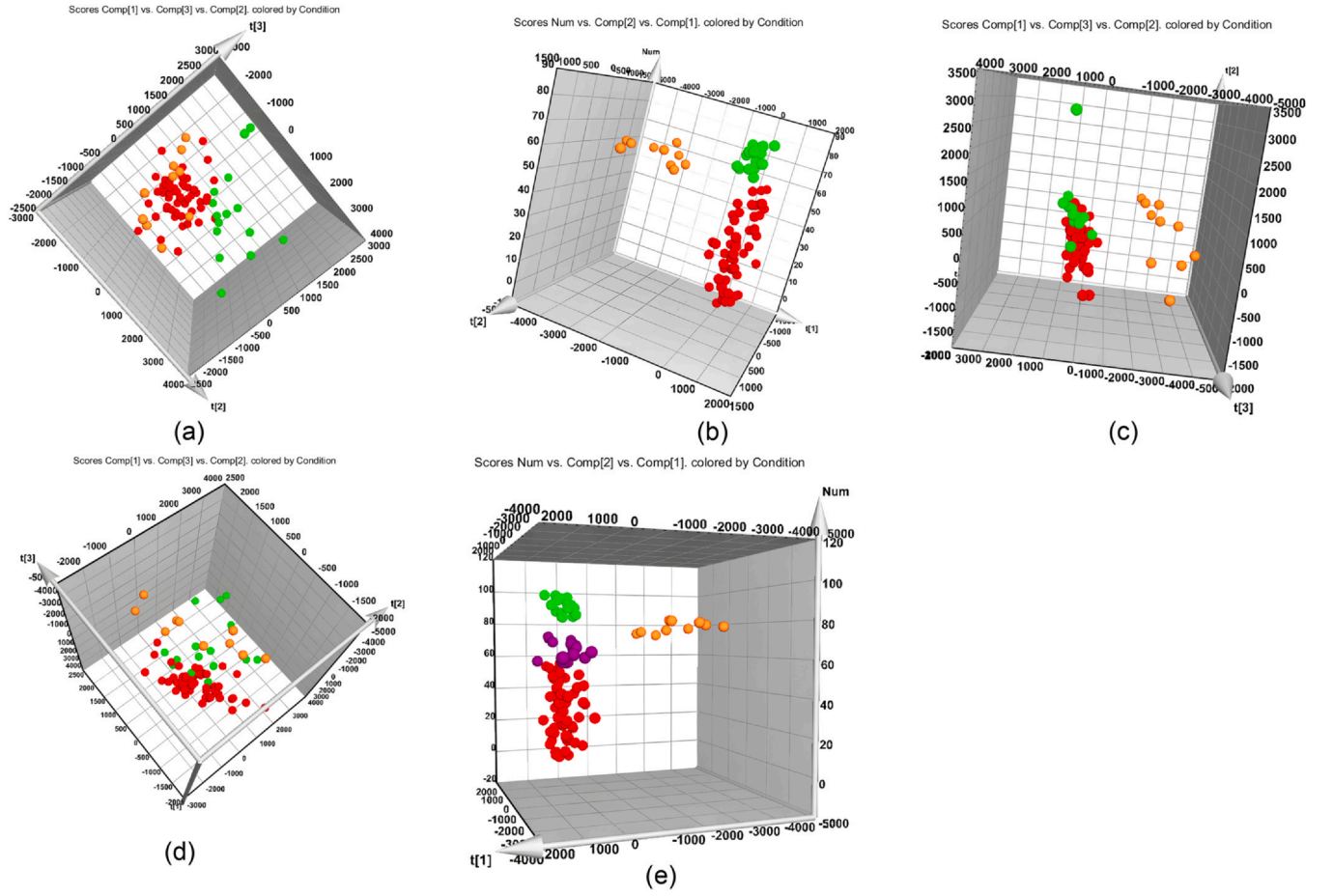

Fig. 4. Serum metabolic profiles of Simiao Yong'an Decoction treatment in diabetic toot patients. Note: K:Normal group,Q:Debridement group,ZLQ:Debridement group and Chinese medicine group,X:Western medicine group,Z:Chinese medicine group,ZX:Chinese and Western medicine group. (A) Serum metabolic profiles of the normal group, pre-treatment group, and debridement group; (B) Serum metabolic profiles of the normal group, pre-treatment group, and Western medicine group; (C) Serum metabolic profiles of the normal group, pre-treatment group, and traditional Chinese medicine (TCM) group; (D) Serum metabolic profiles of the normal group, pre-treatment group, and combined treatment (Western medicine + TCM) group; (E) Serum metabolic profiles of the normal group, pre-treatment group, Western medicine group, and combined treatment group.

using network pharmacology to study the pharmacodynamic material basis and targets of SYD for DF.

Serum metabolic profile of SYD treatment of DF patients

The metabolic profile score plot showed good clustering of serum metabolic profiles in each group (Fig. 4). Compared to the pre-treatment group, the debridement and TCM groups showed no significant difference, while the Western medicine and combined treatment groups showed significant difference as compared to the pre-treatment group, and displayed a trend toward normalization, indicating that both Western medicine and combined treatment could correct metabolic disturbances in DF patients, with the combined treatment showing stronger effects.

Clustering of serum biomarkers in SYD treatment of DF patients

As shown in Fig. 5, there was good clustering of serum differential metabolites among groups, indicating differences in these biomarkers between groups.

Effects of SYD on blood biomarkers in DF patients

By comparing relative peak areas, 18 serum differential metabolites in DF patients showed no significant regulation in the debridement group. In the TCM group, the serum content of one metabolite, uric acid, was significantly reduced ($P < 0.05$). In the Western medicine group, 2 serum metabolites, LysoPA (0:0/18:2(9Z,12Z)) and LysoPC (O-18:0), were significantly reduced ($P < 0.05$). In the combined treatment group, metabolites including uric acid, dCMP, LysoPA (0:0/18:2 (9Z,12Z)), uridine 5'-diphosphate, and LysoPC (O-18:0) were significantly reduced, with relative peak areas shown in Fig. 6. This suggests that SYD may intervene in the development of DF by regulating these metabolites' biological pathways.

Metabolic pathway analysis of SYD treatment of DF patients

The metabolic pathways of the 4 serum differential metabolites regulated by SYD were analyzed, and the results showed that SYD could treat DF by regulating glycerophospholipid metabolism, pyrimidine metabolism, glycosylphosphatidylinositol (GPI) anchor biosynthesis, arginine biosynthesis, glycerolipid metabolism, pantothenate and CoA biosynthesis, ether lipid metabolism, phosphatidylinositol signaling system, glutathione metabolism, and alanine, aspartate, and glutamate metabolism (Fig. 7).

Integration of metabolomics and network pharmacology in SYD treatment of DF

The 9 differential metabolites in SYD treatment for DF patients were integrated with the 20 core target genes obtained from network pharmacology using Metascape software. The results showed significant enrichment in bile acid biosynthesis, glycerophospholipid metabolism,

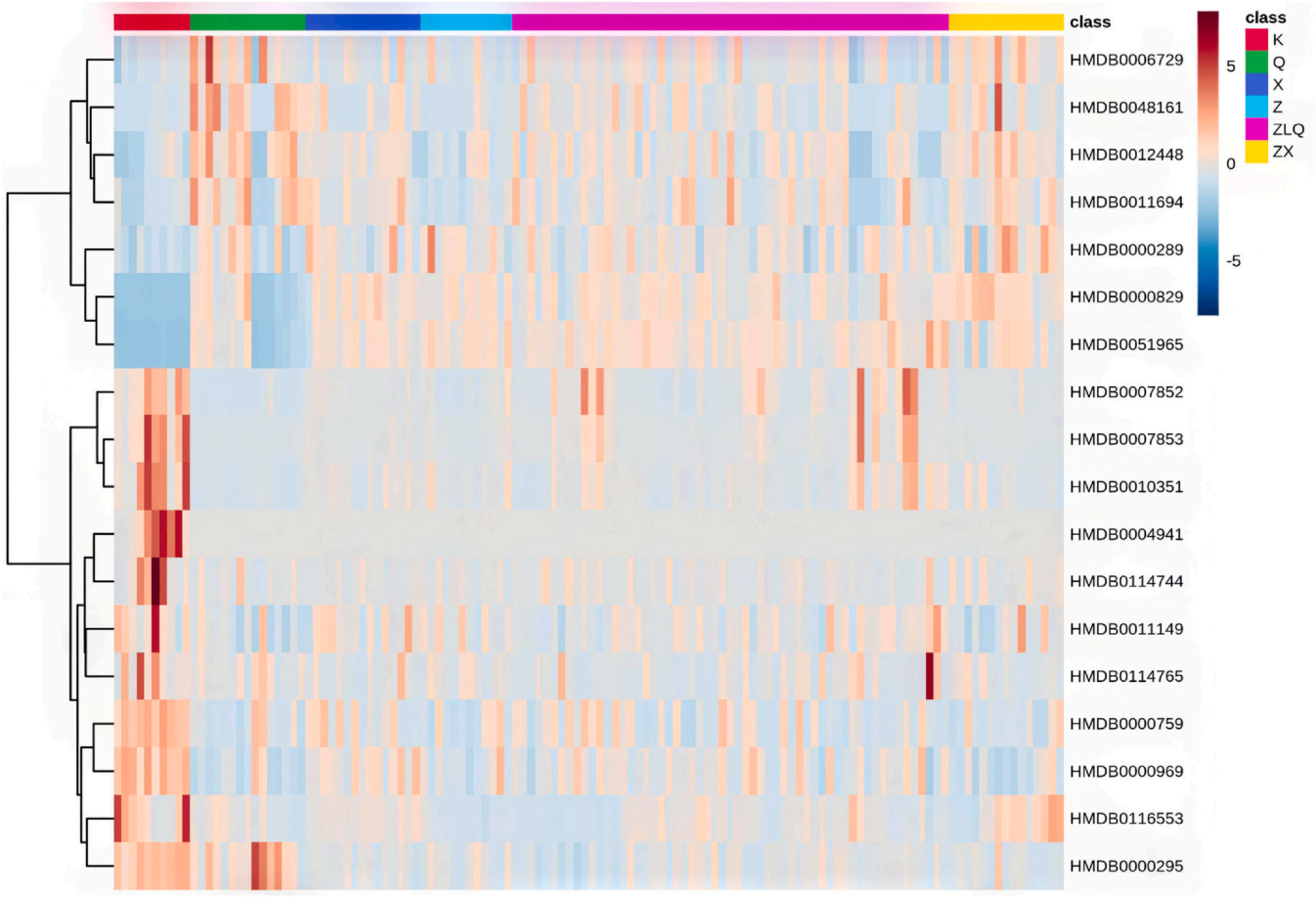

Fig. 5. Hierarchical clustering heatmap of serum biomarkers in diabetic foot patients treated with Simiao Yong'an Decoction.

sphingolipid biosynthesis, histidine metabolism, purine metabolism, and pyrimidine metabolism pathways.

Discussion

In recent years, modern scientific methods have been extensively used to study TCM, revealing that TCM has multi-component, multi-pathway, and multi-target synergistic effects, making the study of its pharmacodynamic material basis and mechanisms more complex.[16] With the development of modern medical science, network biology has provided new insights into the mechanisms of TCM, and network pharmacology, integrating systems biology, multi-directional pharmacology, and bioinformatics, has emerged as a research model. Its systemic and holistic characteristics align with the holistic view of TCM formulation.[17]

This study combined metabolomics and network pharmacology to explore the active components, targets, and metabolic pathways of SYD. Using databases and software such as TCMSP, GeneCards, OMIM, TTD, Uniprot, PDB, String, Metascape, Cytoscape, AutoDockTools, and PyMOL, we summarized the effective components, targets, and metabolic pathways of SYD. Based on the PPI regulatory network of SYD, we identified 20 targets with strong correlations to other drug targets and conducted further research. KEGG pathway enrichment indicated that SYD may treat DF through the MAPK, TNF, PI3K-Akt, HIF-1, and Toll-

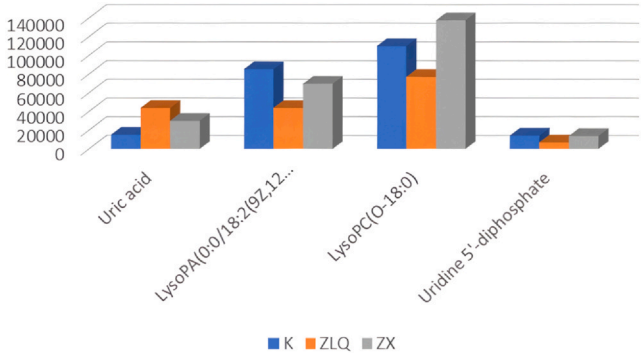

Fig. 6. Relative peak areas of serum biomarkers in diabetic foot patients treated with Simiao Yong'an Decoction.

like receptor signaling pathways, with the phosphatidylinositol signaling pathway consistent with the metabolic pathways involved in SYD intervention in DF patients, further supporting SYD's role in improving DF injury through the phosphatidylinositol metabolic pathway.

The phosphatidylinositol pathway plays a crucial role in human DF. It is an intracellular signal transduction pathway mediated by serine or threonine phosphorylation of downstream substrates. By responding to extracellular

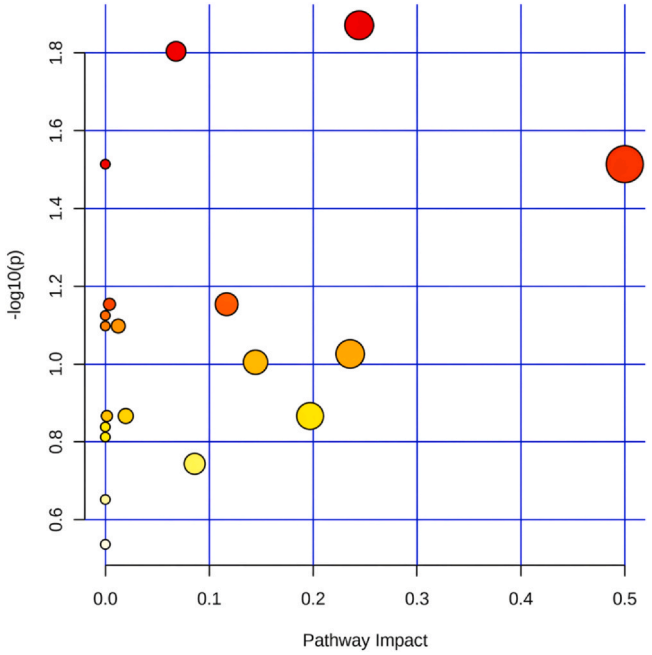

Fig. 7. Metabolic pathways involved in Simiao Yong'an Decoction treatment for diabetic foot patients.

signals, it promotes metabolism, cell survival, growth, and angiogenesis. The activation of metabolic pathway-related signaling proteins plays a central role in controlling nutrient homeostasis and organ survival, potentially serving as a fundamental mechanism for human metabolic syndrome. It is activated by receptor tyrosine kinases (RTKs) and regulated by genes encoding phosphatidylinositol 3-kinase R1, R2, and R3.[18]

Conclusion

In summary, the mechanism of SYD in treating DF may involve regulating the phosphatidylinositol signaling pathway, inducing the production of phosphatidylinositol 3-kinase, stimulating the generation of phosphatidylinositol triphosphate, inhibiting the metabolism of phosphatidylcholine and phosphatidylethanolamine, increasing insulin sensitivity, and improving pancreatic secretion disorders, effectively alleviating lipid metabolism disorders in DF patients. The study of SYD in reducing DF damage integrates TCM's holistic approach with modern medicine, offering a personalized and comprehensive treatment model that will undoubtedly become a future direction in medical development.

Declarations

Not applicable.

Authors' contributions

K. Zhang: Project leader, Project Research and development. B. Zhang: Network pharmacological analysis and paper writing. Q. Wu: Network pharmacological analysis, databases and software are TCMSP, geneCards, OMIM, and TTD. S. Zhu: Blood and urine samples were systematically collected from the participants. D. Wang: Systematic collection of blood metabolomics data. C. Zhang: Systematic collection of urine metabolomics data.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Heilongjiang Provincial Hospital (SYYLLBA2022037). All procedures involving human participants were conducted in accordance with the ethical standards set by the institutional and national research committees and with the 1964 Helsinki Declaration and its subsequent amendments or comparable ethical standards. Informed consent was obtained from all participants before participation in the study.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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Declarations of Competing interests

The authors declare that they have no competing interests.

Acknowledgements

Not applicable.

Authors' other information

Not applicable.

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