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Metabolomics-Based Study on the Mechanism of Simiao Yong' an Decoction for Diabetic Foot (Postprint)

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Date: 2025-07-09T15:00:02+00:00

Abstract

Background In recent years, diabetic foot has become a significant cause of disability and mortality among diabetic patients. With advancements in era and technology, the understanding and research of diabetic foot in both modern medicine and traditional Chinese medicine have gradually deepened, further improving therapeutic approaches for diabetic foot, which can alleviate patient suffering to a certain extent and enhance their quality of life. Objective To investigate the mechanism of action of Simiao Yong' an Decoction in treating diabetic foot through a combined approach of metabolomics and network pharmacology. Methods Diabetic foot patients hospitalized in the Department of Burns, Department of Vascular Surgery, and Department of Vascular Surgery at Nangang Campus of Heilongjiang Provincial Hospital from July 2023 to August 2024 were selected as study subjects. This study included a total of 60 diabetic foot patients meeting the criteria of excessive heat-toxin syndrome. They were randomly divided into a debridement group, Western medicine group, Chinese medicine group, and combined Chinese-Western medicine group, with 15 cases in each group, and an additional 15 healthy individuals were included as a control group. Firstly, databases and software including TCMSP, GeneCards, OMIM, and TTD were utilized to identify the pharmacodynamic basis, therapeutic targets, and metabolic pathways of Simiao Yong'an Decoction for diabetic foot. Furthermore, an integrated study of the serum metabolomics and network pharmacology of Simiao Yong' an Decoction was conducted to verify the potential active components and metabolic pathways through which Simiao Yong' an Decoction intervenes in diabetic foot. Results The main active components of Simiao Yong' an Decoction for treating diabetic foot include luteolin, quercetin, and formononetin, among others; it may treat diabetic foot by regulating pathways such as the mitogen-activated protein kinase signaling pathway, tumor necrosis factor signaling pathway, phosphatidylinositol signaling pathway,

HIF-1 signaling pathway, and Toll-like receptor signaling pathway, through targets including AKT1, TNF, HSP90AA1, MAPK8, and STAT3, among which the phosphatidylinositol signaling pathway is consistent with the findings from serum metabolomics studies of Simiao Yong' an Decoction. Conclusion The phosphatidylinositol signaling pathway may represent the metabolic pathway through which Simiao Yong' an Decoction intervenes in diabetic foot.

Full Text

Research on the Mechanism of Action of Simiao Yongan Decoction in the Treatment of Diabetic Foot Based on Metabolomics

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Abstract

Background: In recent years, diabetic foot has become a major cause of disability and mortality among diabetic patients. With the advancement of modern science and technology, both modern medicine and traditional Chinese medicine have deepened their understanding and research of diabetic foot, leading to improved treatment approaches that can alleviate patient suffering and enhance quality of life.

Objective: This study aims to investigate the mechanism of action of Simiao Yongan Decoction in treating diabetic foot through an integrated metabolomics and network pharmacology approach.

Methods: Diabetic foot patients hospitalized in the Burn Department, Vascular Surgery Department of Heilongjiang Provincial Hospital, and the Vascular Surgery Department of Nangang Campus from July 2023 to August 2024 were selected as study subjects. A total of 60 patients with heat-toxin intense type diabetic foot meeting the criteria were randomly divided into four groups: debridement group, Western medicine group, traditional Chinese medicine group, and combined Chinese-Western medicine group, with 15 cases in each group. An additional 15 healthy individuals were included as a control group. Databases and software including TCMSP, GeneCards, OMIM, and TTD were utilized to identify the pharmacodynamic basis, therapeutic targets, and metabolic pathways of Simiao Yongan Decoction for diabetic foot. The serum metabolomics

and network pharmacology of Simiao Yongan Decoction were integrated to validate potential active components and metabolic pathways.

Results: The main active components of Simiao Yongan Decoction for treating diabetic foot include luteolin, quercetin, and formononetin. The decoction may treat diabetic foot by regulating pathways such as the mitogen-activated protein kinase signaling pathway, tumor necrosis factor signaling pathway, phosphatidylinositol signaling pathway, HIF-1 signaling pathway, and Toll-like receptor signaling pathway through targets including AKT1, TNF, HSP90AA1, MAPK8, and STAT3. Notably, the phosphatidylinositol signaling pathway was consistent with the serum metabolomics findings of Simiao Yongan Decoction.

Conclusion: The phosphatidylinositol signaling pathway may represent the key metabolic pathway through which Simiao Yongan Decoction intervenes in diabetic foot.

Keywords: diabetic foot; Simiao Yongan Decoction; metabolomics; network pharmacology; metabolic pathway; phosphatidylinositol

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1. Materials and Methods

1.1 Databases, Platforms, and Software

The databases, platforms, and software used in this study are detailed in Table 1 .

1.2 Main Instruments and Reagents

Instruments: Waters ACQUITY UPLC ultra-high performance liquid chromatograph (Waters, USA), Waters Premier LCT XE mass spectrometry system (Waters, USA), Masslynx 4.1 software workstation, Sorvall ST 16R benchtop centrifuge (Thermo Scientific, USA), KQ-500DB ultrasonic cleaner (Kunshan Ultrasound Instrument Co., Ltd.), Nichipet EX micro-sampler (10-100 L, 100-1000 L, NICHIRYO, Japan), VX-II multi-tube vortex oscillator (Beijing Tajin Technology Co., Ltd.), Thermo Scientific 995 ultra-low temperature freezer (Thermo Scientific, USA).

Reagents: Leucine enkephalin (LE) calibration solution and sodium formate calibration solution (Sigma, USA), chromatographic acetonitrile (Thermo, USA), ultrapure water (Guangzhou Watsons Food & Beverage Co., Ltd., China), chromatographic methanol and chromatographic formic acid (Dikma, USA), with all other reagents being analytical grade.

1.3 Study Subjects

Diabetic foot patients hospitalized in the Burn Department, Vascular Surgery Department of Heilongjiang Provincial Hospital, and the Vascular Surgery De-

partment of Nangang Campus from July 2023 to August 2024 were selected as study subjects. The study included 60 patients with heat-toxin intense type diabetic foot meeting the criteria, randomly divided into debridement group, Western medicine group, traditional Chinese medicine group, and combined Chinese-Western medicine group (15 cases each). An additional 15 healthy individuals served as the control group. This study was approved by the Medical Ethics Committee of Heilongjiang Provincial Hospital (Approval No.: SYYLLBA2022037), and all patients and their families provided informed consent.

Inclusion Criteria: (1) Diabetic foot diagnosis according to the "Chinese Guidelines for the Diagnosis and Treatment of Diabetic Foot" ; (2) Wagner grade 1 or 2 classification; (3) Patients requiring surgical debridement who could tolerate and agreed to surgery; (4) Age 30-70 years.

Exclusion Criteria: (1) Other special types of diabetes or gestational diabetes; (2) Acute diabetic complications within the past month; (3) Comorbid respiratory, digestive, hematological, rheumatologic, or immune system diseases, thyroid disease, tuberculosis, or cancer; (4) Abnormal liver or kidney function, polyarteritis, arterial embolism, or Raynaud's disease; (5) Participation in other clinical trials or use of hormone drugs affecting metabolism within 3 months; (6) Psychiatric disorders, cognitive impairment, or limited civil capacity; (7) Pregnant or lactating women; (8) Poor compliance or incomplete data.

1.4 Network Pharmacology Analysis of Simiao Yongan Decoction Targets and Pathways

1.4.1 Pharmacodynamic Basis and Target Identification: The TCMSP database was searched using keywords: Honeysuckle, Scrophularia, Angelica, Licorice. Components with oral bioavailability (OB) 30% and drug-likeness (DL) 18% were screened, supplemented by literature review. All screened components were input into TCMSP to predict targets, which were then converted to gene names using the Uniprot database to obtain Simiao Yongan Decoction-related targets.

1.4.2 Disease-Related Target Acquisition: GeneCards, OMIM, and TTD databases were searched for "diabetic foot." Candidate targets were filtered using reviewed and HUMAN sources. GeneCards targets were further screened using the MEDIAN function based on relevance scores until the number fell below 2,000. Final targets were integrated and duplicates removed, yielding disease-related targets.

1.4.3 Protein-Protein Interaction Network Construction: The intersection of traditional Chinese medicine and disease-related targets was imported into the String platform with a minimum interaction score of 0.9 and organism set to "Homo sapiens," hiding disconnected nodes. The output tsv file was processed to obtain 126 potential targets for Simiao Yongan Decoction in treating diabetic foot. Cytoscape 3.8.0 with the "cytoHubba" plugin identified 20

high-value potential targets.

1.4.4 "Herb-Active Component-Potential Target" Network Construction: Active components associated with potential targets were integrated with herbal potential targets and processed in Cytoscape 3.8.0 to obtain the network. The "Analyze Network" function calculated topological parameters, and the top 10 active components were selected as core components.

1.4.5 GO and KEGG Pathway Enrichment Analysis: Potential targets were imported into Metascape Platform with parameters: Min Overlap = 3, P Value Cutoff = 0.01, Min Enrichment = 1.5. GO Molecular Functions (GO-MF), GO Biological Processes (GO-BP), GO Cellular Components (GO-CC), and KEGG Pathway analyses were performed, with results visualized in RStudio.

1.4.6 Molecular Docking: PDB format files of core target proteins were downloaded from PDB database, and mol2 format files from TCMSP. AutoDockTools-1.5.6 was used for processing (removing ligands, water, hydrogenation, charging) and storage in pdbqt format. AutoDockVina performed molecular docking, with Pymol used for visualization.

1.5 Integrated Serum Metabolomics and Network Pharmacology Study

1.5.1 Sample Processing: Serum samples were thawed at 4°C. 200 L of sample was mixed with 3 volumes of pre-cooled methanol (-20°C), vortexed for 30 seconds, left at room temperature for 10 minutes to precipitate proteins, then centrifuged at 14,000 rpm for 20 minutes. The supernatant was transferred to sample vials for analysis.

1.5.2 Chromatographic and Mass Spectrometry Conditions: - **Chromatography:** Waters ACQUITY UPLC BEH C18 column (1.8 m, 2.1×100 mm) with mobile phase A (acetonitrile with 0.1% formic acid) and B (ultrapure water with 0.1% formic acid). Column temperature: 40°C; sample temperature: 4°C; flow rate: 0.4 mL/min; injection volume: 5 L. Gradient elution conditions are shown in Table 2 . - **Mass Spectrometry:** Waters Premier LCT XE system with electrospray ionization (ESI) in negative ion mode. Capillary voltage: 1,500 V; cone voltage: 60 V; source temperature: 110°C; desolvation temperature: 360°C; desolvation gas flow: 750 L/h; cone gas flow: 20 L/h. Full scan range: m/z 100-1,500 amu with LE real-time correction (1 ng/mL, 0.04 mL/min).

1.5.3 Metabolic Profiling Analysis: Processed serum samples were analyzed in negative ion mode. Mass spectrometry data were imported into Waters Progenesis QI 2.3 software for peak extraction, alignment, deconvolution, and normalization to obtain three-dimensional data (retention time, m/z, peak intensity). EZinfo 3.0 software performed principal component analysis (PCA) and orthogonal partial least squares discriminant analysis (OPLS-DA).

1.5.4 Identification of Differential Metabolites: Retention time and m/z

information of differential metabolites were imported into Progenesis QI 2.3 identification module. Using HMDB database with 2 mDa mass tolerance, theoretical fragments were matched with IDA data for structural identification. Validation was performed using HMDB, KEGG, Massbank, and Metlin databases combined with MS/MS data.

1.5.5 Biological Information Analysis: Differential metabolites and metabolic pathways were summarized and classified. Literature searches on biomarkers, diseases, and targets were conducted to analyze biological significance and elucidate mechanisms.

1.5.6 Metabolic Pathway Analysis: Differential metabolite names and KEGG/HMDB IDs were imported into Metaboanalyst (http://www.metaboanalyst.ca/) for pathway analysis.

1.5.7 Integration of Metabolomics and Network Pharmacology: Nine differential metabolites from Simiao Yongan Decoction intervention were integrated with 20 core target genes from network pharmacology using Metascape software.

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2. Results

2.1 Network Pharmacology Results

2.1.1 Pharmacodynamic Basis and Targets: Simiao Yongan Decoction yielded 115 active components: 19 from Honeysuckle, 7 from Scrophularia, 5 from Angelica, and 90 from Licorice after removing duplicates.

2.1.2 Disease-Related Targets: From GeneCards (4,682 targets), OMIM (95 targets), and TTD (11 targets), 1,203 targets were initially obtained. After secondary screening (Relevance score 6.497622013), 1,172 targets were retained, resulting in 203 disease-related targets after integration and deduplication.

2.1.3 PPI Network Construction: The intersection of herbal and disease targets yielded 136 targets, which were filtered through String platform to obtain 126 potential targets. The PPI network contained 126 nodes and 672 edges [FIGURE:1]. The top 20 potential targets ranked by degree were: STAT3, AKT1, JUN, MAPK3, MAPK1, TNF, RELA, TP53, IL6, HSP90AA1, MAPK8, VEGFA, MAPK14, EGFR, APP, FOS, MYC, CXCL8, ESR1, EGF.

2.1.4 Herb-Active Component-Target Network: The network contained 237 nodes (4 herbs, 107 active components, 126 potential targets) and 1,211 edges

. The top 10 active components were: MOL000006 (luteolin), MOL000098 (quercetin), MOL000358 (-sitosterol), MOL000392 (formononetin), MOL000422 (kaempferol), MOL001789 (isoliquiritigenin), MOL003896 (7-methoxy-2-methylisoflavone), MOL004328 (naringenin), MOL002773 (-carotene),

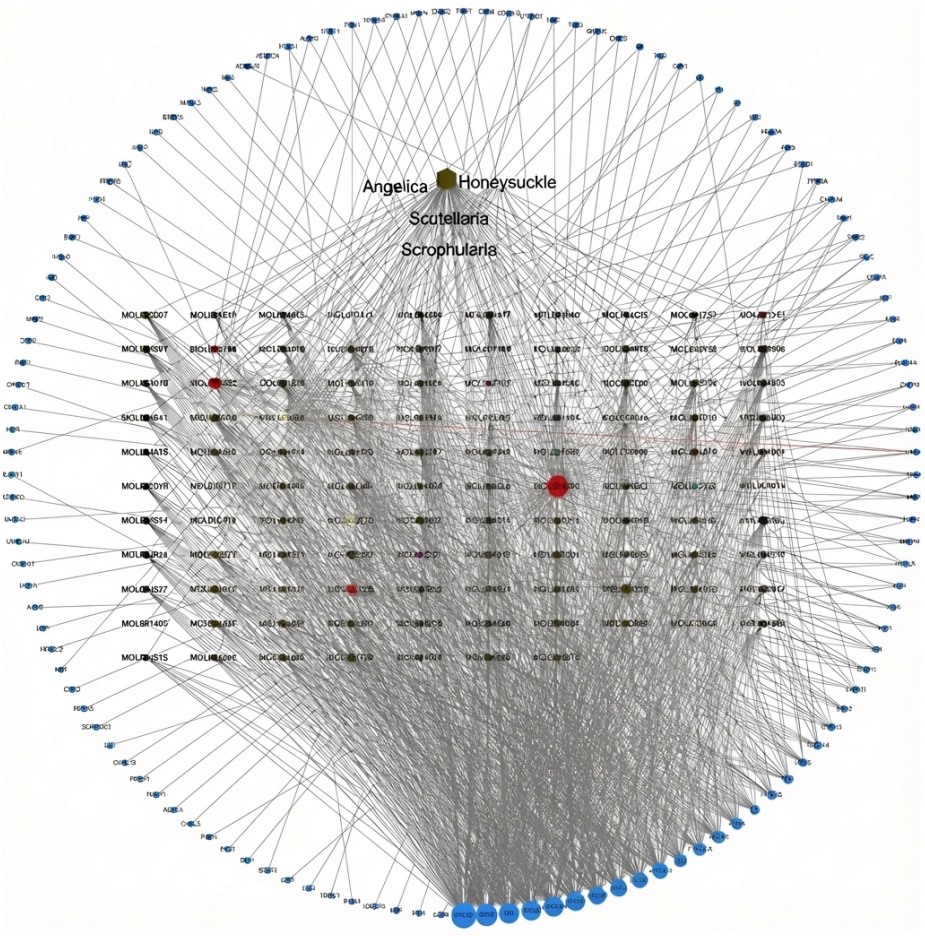

Figure 1: Figure 2

MOL000497 (licochalcone A).

2.1.5 GO and KEGG Enrichment Analysis: Metascape analysis yielded 143 GO-MF terms, 2,401 GO-BP terms, 115 GO-CC terms, and 209 KEGG pathways. The top 40 terms with smallest LogP values were visualized [FIGURE:3]. GO-MF enrichment indicated anti-diabetic foot effects, while GO-CC suggested mechanisms related to membrane rafts, membrane regions, vesicle lumen, and cytoplasmic vesicle lumen. KEGG pathways included AGE-RAGE signaling, fluid shear stress and atherosclerosis, phosphatidylinositol metabolism, IL-17 signaling, MAPK signaling, TNF signaling, PI3K-Akt signaling, HIF-1 signaling, Th17 cell differentiation, apoptosis, T cell receptor signaling, Toll-like receptor signaling, and FoxO signaling.

2.1.6 Molecular Docking: Sixty molecular docking results were obtained. Except for RELA, all core targets showed good binding activity with core components (average binding energy: -7.06 kcal/mol), validating the network pharmacology approach.

2.2 Integrated Metabolomics and Network Pharmacology Results

2.2.1 Serum Metabolic Profiling: PCA score plots showed distinct metabolic profiles among groups. Compared with pre-treatment, debridement and Chinese medicine groups showed indistinct separation, while Western medicine and combined groups showed significant separation from pre-treatment with a trend toward the control group, indicating correction of metabolic disturbances [FIGURE:4].

2.2.2 Biomarker Clustering: Hierarchical clustering heatmap revealed that serum differential metabolites clustered well among groups, demonstrating distinct biomarker patterns [FIGURE:5].

2.2.3 Effects on Blood Biomarkers: Among 18 differential metabolites, the debridement group showed no significant regulation. The Chinese medicine group significantly regulated 1 metabolite (uric acid, $P<0.05$). The Western medicine group significantly regulated 2 metabolites (lysophosphatidic acid A [0:0/18:2(9Z,12Z)] and lysophosphatidic acid C (O-18:0), $P<0.05$). The combined group significantly regulated 4 metabolites (uric acid, deoxycytidine monophosphate, lysophosphatidic acid A [0:0/18:2(9Z,12Z)], uridine 5' -diphosphate, and lysophosphatidic acid C (O-18:0)) [FIGURE:6].

2.2.4 Metabolic Pathway Analysis: Simiao Yongan Decoction may treat diabetic foot by regulating glycerophospholipid metabolism, pyrimidine metabolism, GPI-anchor biosynthesis, arginine biosynthesis, histidine metabolism, triacylglycerol metabolism, pantothenate and CoA biosynthesis, ether lipid metabolism, phosphatidylinositol signaling, glutathione metabolism, and alanine/aspartate/glutamate metabolism [FIGURE:7, Table 1].

2.2.5 Integration of Metabolomics and Network Pharmacology: Integration of 9 differential metabolites with 20 core target genes revealed significant

enrichment in bile acid biosynthesis, glycerophospholipid metabolism, sphingolipid metabolism, histidine metabolism, purine metabolism, and pyrimidine metabolism pathways.

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3. Discussion

Recent research using modern scientific techniques has revealed that traditional Chinese medicine features multi-component, multi-pathway, and multi-target synergistic effects, making pharmacodynamic studies more complex. Network pharmacology, integrating systems biology, polypharmacology, and bioinformatics, provides new insights into traditional Chinese medicine mechanisms and aligns with the holistic concept of herbal formulation.

This study combined metabolomics and network pharmacology to systematically analyze Simiao Yongan Decoction. The PPI network identified 20 core targets. KEGG pathway enrichment indicated that Simiao Yongan Decoction may treat diabetic foot through MAPK, TNF, PI3K-Akt, HIF-1 signaling, and Toll-like receptor pathways. The phosphatidylinositol signaling pathway was consistent with metabolomics results, suggesting this pathway may be key to the decoction' s therapeutic effects.

The phosphatidylinositol pathway is an important intracellular signal transduction pathway in human diabetic foot. Activated by receptor tyrosine kinases, it is regulated by phosphatidylinositol 3-kinase genes (PIK3R1, PIK3R2, PIK3R3). This pathway plays a central role in controlling nutrient homeostasis and organ survival, potentially underlying metabolic syndrome mechanisms.

This study first identified specific targets and pathways through network pharmacology, then validated these through serum metabolomics of diabetic foot patients. The consistent results suggest that Simiao Yongan Decoction may regulate the phosphatidylinositol signaling pathway, induce phosphatidylinositol 3-kinase production, promote phosphatidylinositol triphosphate generation, inhibit phosphatidylcholine and phosphatidylethanolamine metabolites, increase insulin sensitivity, improve pancreatic secretion dysfunction, and effectively alleviate lipid metabolism disorders in diabetic foot patients.

The integration of traditional Chinese medicine holistic concepts with modern medicine represents a personalized, three-dimensional treatment approach that will become a future direction in medical development.

Author Contributions

ZHANG Kexing conceived the research idea and designed the experimental protocol. ZHANG Bo was responsible for the entire network pharmacology experimental design and manuscript writing. WU Qiong performed specific

data analysis and experimental plotting using TCMSP, GeneCards, OMIM, and TTD software. ZHU Shanshan collected serum samples and performed sample processing for metabolomics. ZHANG Chunnan collected serum samples and conducted experimental data analysis.

Funding: Heilongjiang Provincial Administration of Traditional Chinese Medicine Research Project (ZHY2022-066)

Conflict of Interest: The authors declare no conflict of interest.

Citation: ZHANG K X, ZHANG B, WU Q, et al. Research on the mechanism of action of Simiao Yongan Decoction in the treatment of diabetic foot based on metabolomics[J]. Chinese General Practice, 2025. DOI: 10.12114/j.issn.1007-9572.2024.0676. [Epub ahead of print].

Original Publication: This article first appeared in Precision Medication 2025, Issue 2 (https://doi.org/10.1016/j.prmedi.2025.100028)

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Received: February 14, 2025 **Revised:** May 26, 2025 **Editor:** KANG Yanhui

Figures

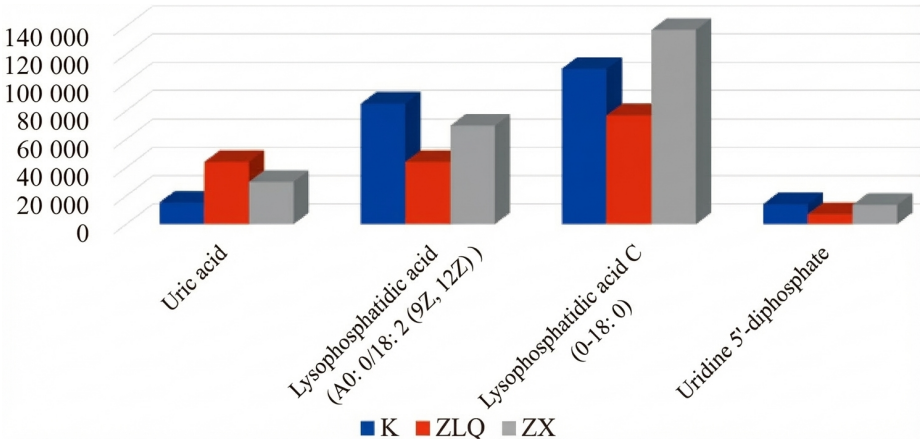

Figure 2: Figure 13

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