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Network Pharmacology and Molecular Docking Analysis of Zisheng Decoction for Diabetic Gastroparesis: Mechanism Exploration

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Abstract: ***Objective:*** *The primary goal of the current research was to investigate the bioactive constituents, candidate therapeutic targets, and underlying therapeutic mechanisms of Zisheng Decoction (ZSD) in the treatment of diabetic gastroparesis (DGP). This was achieved by applying a combined approach of network pharmacology and molecular docking simulations.* ***Methods:*** *Information regarding the bioactive compounds of ZSD and their corresponding targets was mined from multiple pharmacological databases. Simultaneously, gene targets associated with DGP were obtained utilizing the OMIM and GeneCards datasets. We constructed a protein-protein interaction (PPI) network to analyze intersecting targets and utilized Cytoscape to screen for hub genes. Furthermore, functional roles and involved signaling routes were mapped via enrichment analysis of GO and KEGG. Finally, the interactive potential between the primary constituent compounds and their primary targets was validated using molecular docking techniques.* ***Results:*** *A total of 46 active compounds and 593 predicted targets related to Zisheng Decoction (ZSD) were identified, along with 252 targets associated with diabetic gastroparesis (DGP). Then, we intersected 46 bioactive compounds, 593 putative targets, and 252 disease-associated targets to obtain 13 shared targets, of which GCK, PPARG, INSR, AKR1B1 and PDGFRA were considered to be potential key therapeutic targets based on degree centrality and functional relevance. Gene Ontology (GO) enrichment analysis indicated that most targets were significantly associated with biological processes involving glucose balance and insulin secretion. KEGG pathway analysis revealed a primary concentration in the AMPK signaling pathway, type 2 diabetes mellitus, galactose metabolism, and longevity regulation pathways. Furthermore, molecular docking simulations demonstrated that certain active ingredients in ZSD could bind stably and with high affinity to the core targets GCK and PPARG with high affinity.* ***Conclusion:*** *Zisheng Decoction (ZSD) has therapeutic effects on diabetic gastroparesis (DGP) via a mechanism involving multiple targets and pathways, including modulating glucose metabolism, restoring gut motility and mucosal health, ameliorating insulin resistance, and reducing chronic low-grade inflammation. Such results provide a scientific basis for ZSD's clinical application in DGP therapy.*

Keywords: Network pharmacology, Zisheng Decoction, Diabetic gastroparesis, Molecular docking, Mechanism of action.

1. Introduction

Diabetic gastroparesis (DGP) represents one of the most frequent and serious complications associated with diabetes mellitus. Delayed gastric emptying without mechanical obstruction can cause postprandial early satiety, nausea, abdominal distension, and vomiting. Symptoms have a significant impact on nutritional intake, blood glucose levels, and quality of life [1]. About 25% of patients with diabetes have gastroparesis, its risk increasing with disease duration and poor glycemic control [2]. However, currently available treatments (intensive glucose control, prokinetic drugs like metoclopramide and erythromycin, diet therapy, etc.) are

often ineffective, lead to symptom relapse, and cause side effects such as tardive dyskinesia or QT interval prolongation [3]. Therefore, new, safe, and pathogenetically based options are needed.

Accordingly, under the framework of TCM theories, DGP belongs to the TCM diagnoses of Piman (upper abdominal distension and fullness) and Outu (nausea and vomiting). It can be classified into Xiaoke (consumptive thirst disease) syndrome from the perspective of the TCM syndrome [4]. The pathogenesis of this disease usually involves spleen-stomach qi deficiency, which may also be mixed with yin deficiency, internal heat, and secondary qi stagnation and dampness obstruction. ZSD was first reported in Zhang Xichun's *Combined Treatment of Traditional Chinese Medicine and Western Medicine*, and is composed of five different Chinese medicinal materials: *Dioscorea opposita, Scrophularia ningpoensis, Atractylodes macrocephala, Endothelium Corneum Gigeriae Galli* (Gallus gallus domesticus, processed chicken gizzard membrane), and *Arctium lappa*. In practice, doctors prescribe ZSD for the purpose of reinforcing spleen-qi, nourishing yin, removing deficient heat, and generating body fluid. These effects are consistent with the theoretical etiology of DGP in TCM. Recent preliminary experiments and clinical trials have shown that ZSD has the functions of promoting gastric motility, relieving postprandial symptoms, improving glycemic control, and repairing gastric mucosa [5−7]. Yet, there remains insufficient understanding about its molecular mechanisms at the system level. Accordingly, to investigate the potential pharmacologic basis for its therapeutic effects against DGP, we formulated an integrated research program using the approaches of network pharmacology and molecular docking in this present study.

2. Materials and Methods

2.1 Screening of Bioactive Ingredients and Targets in ZSD

To obtain the active ingredients of ZSD, we utilized the TCMSP (Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform). First, we screened candidates using two primary pharmacokinetic filters, specifically requiring oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18. These are standard thresholds for estimating in vivo absorption and compound tractability. For Gallus gallus domesticus, whose chemical constituents are not comprehensively cataloged in TCMSP, putative targets were predicted using SwissTargetPrediction (probability score > 0.5). All compound-associated targets were unified, and redundant entries were removed to yield a non-redundant set of ZSD-related targets.

2.2 Collection and Curation of DGP-Associated Targets

Disease-related targets: We gathered disease-associated targets from three trusted databases—GeneCards, OMIM (Online Mendelian Inheritance in Man), and TTD (Therapeutic Target Database)—using keywords "diabetic gastroparesis", "gastroparesis AND diabetes", and "diabetic gastric motility disorder". Entries were manually curated to exclude non-human, non-protein, and low-evidence targets (e.g., those supported by only single-source or non-peer-reviewed reports). After deduplication and consensus integration, a high-confidence DGP target dataset was established.

2.3 Network Construction and Topological Analysis

A Venn diagram was used to obtain the overlap among ZSD-derived targets and DGP-associated targets. Compound-target interaction network was built and mapped by Cytoscape 3.10.2. PPI analysis was conducted through STRING (version 11.5, confidence score ≥ 0.4, species: Homo sapiens). We calculated several topological metrics, including degree, betweenness, and closeness centrality. Core targets were identified as those ranked in the top 10% of no less than two indicators.

2.4 Functional Enrichment Analysis

We performed GO and KEGG pathway enrichment analyses using Metascape with default parameters ($p < 0.05$, minimum overlap = 3 genes). The terms with significant difference were sorted according to the adjusted p-value (Benjamini–Hochberg correction), and the results were visualized using Micro Bioinformatics and GraphPad Prism 9.3.

2.5 Molecular Docking Simulation

The optimized three-dimensional structure of kadsurenone (PubChem CID: 101673) was obtained by energy minimization using ChemOffice 20.0 with MMFF94 force field. Crystal structures of key targets—glucokinase (GCK; PDB ID: 3A0I) and peroxisome proliferator-activated receptor gamma (PPARG; The structure for protein Cdk9 (from the P-TEFb complex, PDB ID: 1I7I)) was obtained from the Protein Data Bank, processed using MOE 2019 (at physiological pH, with co-crystallized ligands and water molecules within 5 Å of the binding site removed), and minimized energetically. Docking simulations were executed using MOE 2019's default London dG scoring function, with 30 poses generated per target. Binding affinity (kcal/mol) and interaction patterns—including hydrogen bonds, hydrophobic contacts, and π-stacking—were analyzed for the top-scoring pose of each complex.

3. Results

3.1 Bioactive Compounds and Putative Targets of ZSD

A total of 46 bioactive compounds were detected in the five herbs of ZSD, comprising 16 from *Dioscorea opposita*, 9 from *Scrophularia ningpoensis*, and 7 from *Arctium lappa*. These compounds collectively mapped to 593 non-redundant human protein targets.

3.2 Identification of Shared ZSD–DGP Targets

Literature- and database-driven curation yielded 252 high-confidence DGP-associated targets. Intersection analysis revealed 13 shared targets between ZSD and DGP, including *PPARG*, *GCK*, *INSR*, *AKR1B1* and *PDGFRA* et al. (Figure 1 and 2).

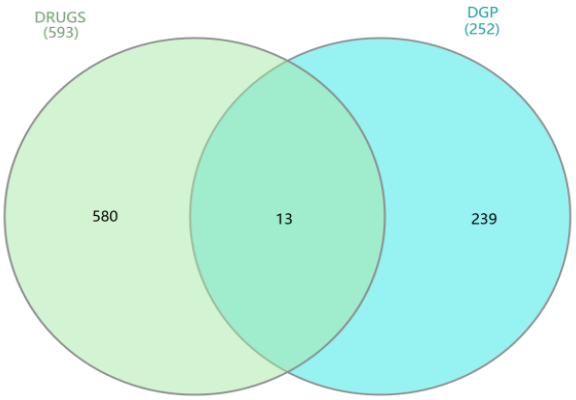

Figure 1: Venn diagram of potential targets of ZSD-DGP

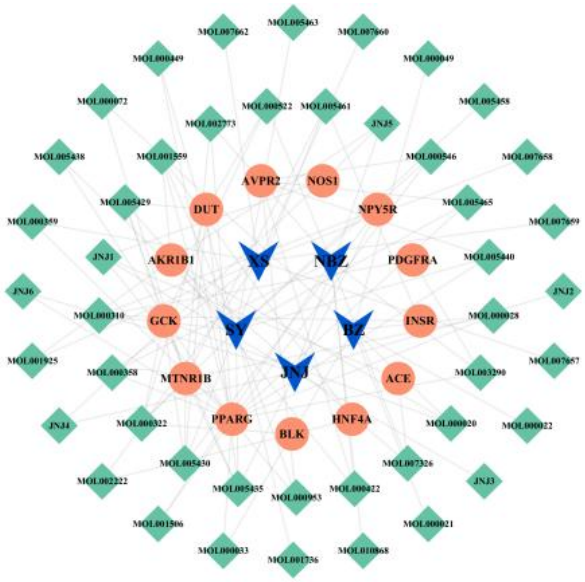

Figure 2: "ZSD active ingredients-DGP predicted targets" network diagram

3.3 PPI Network Topology and Core Target Prioritization

The PPI network comprised 13 nodes and 42 edges. Topological analysis identified *GCK*, *PPARG*, *INSR*, *AKR1B1* and *PDGFRA* as central hubs, exhibiting the highest degree centrality (range: 12–18) and robust connectivity across functional modules. (Figure 3)

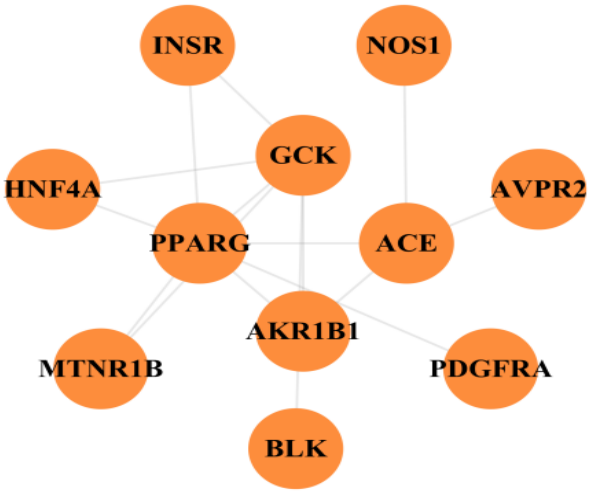

Figure 3: PPI network of ZSD for the treatment of DGP.

3.4 GO and KEGG Enrichment Outcomes

GO enrichment yielded 1,236 significant biological process terms ($p < 0.01$), prominently featuring "regulation of glucose homeostasis", "insulin secretion", "response to oxidative stress", and "regulation of gastrointestinal motility". KEGG analysis identified 83 significantly enriched pathways ($p < 0.01$), most notably the AMPK signaling pathway, type 2 diabetes mellitus, galactose metabolism, insulin resistance, and longevity-regulating pathways. (Figure 4 and 5).

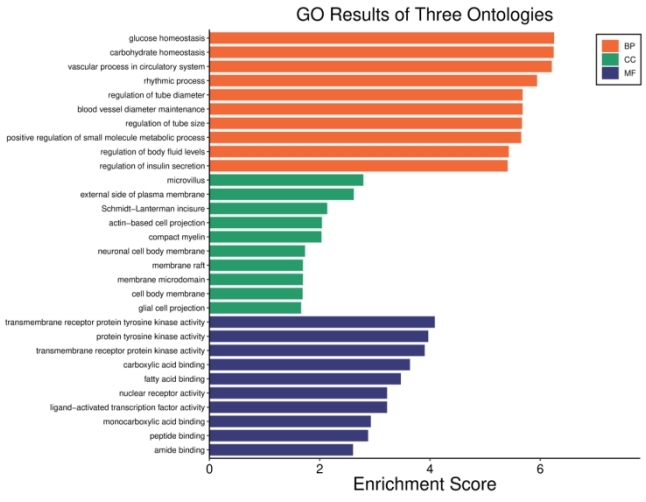

Figure 4: Bar chart of GO analysis results of ZSD in the treatment of DGP

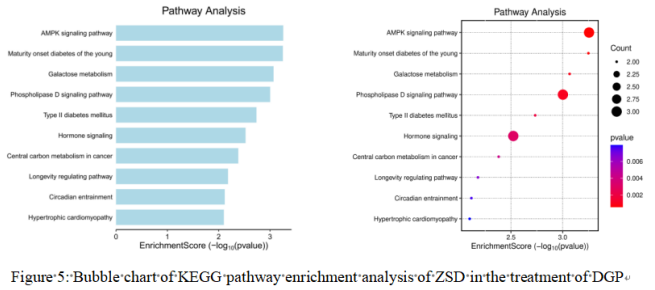

Figure 5: Bubble chart of KEGG pathway enrichment analysis of ZSD in the treatment of DGP

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3.5 Molecular Docking Validation

Kadsurenone exhibited good binding affinities for both GCK (−7.33 kcal/mol) and PPARG (−6.57 kcal/mol) (Table 1). Interaction analysis showed that it could form stable hydrogen bonds with Ser209 and Asn204 in GCK, and with Ser289, His323, and Tyr473 in PPARG, respectively, and had extensive hydrophobic contacts with the binding pockets of each protein, confirming its potential as a dual-target modulator (Figure 6-Figure 7).

Table 1: Binding energy between core components and core targets from molecular docking.

Core Targets	Core Ingredients	Binding Energy (kcal/mol)	PDB ID	Binding Activity Grade
GCK	Kadsurenone	-7.3270	3A0I	Strong binding activity
PPARG	Kadsurenone	-6.5684	1I7I	Good binding activity

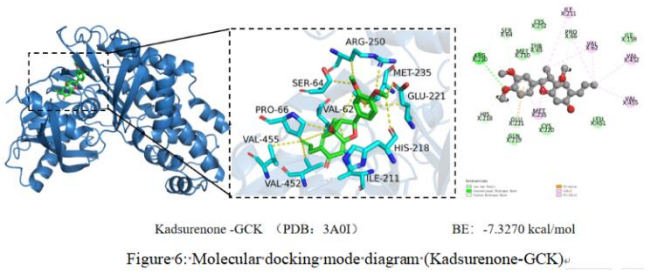

Figure 6: Molecular docking mode diagram (Kadsurenone-GCK)

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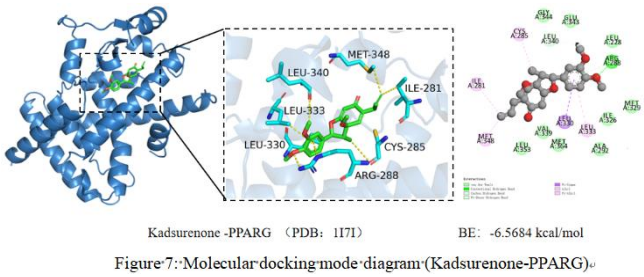

Figure 7: Molecular docking mode diagram (Kadsurenone-PPARG)

4. Discussion

DGP is increasingly recognized as a multifactorial disorder involving insulin resistance, autonomic neuropathy, low-grade neuroinflammation, mitochondrial dysfunction, and enteric glial activation [8–9]. Our integrative analysis positions ZSD as a systems-level intervention targeting two pivotal nodes: GCK, a rate-limiting enzyme in hepatic and pancreatic glucose phosphorylation, which serves as a critical link between carbohydrate metabolism and insulin secretion; and PPARG, a master regulator of adipogenesis and mitochondrial biogenesis, which modulates energy substrate utilization and attenuates inflammatory signaling in gastric smooth muscle and neuronal tissues. Kadsurenone — identified as the key compound bridging both targets in our network analysis—may act synergistically to enhance cellular glucose sensing, restore mitochondrial respiratory capacity, and suppress NLRP3 inflammasome activation, thereby concurrently targeting both metabolic and neuromuscular facets of DGP. The convergence of enriched pathways — including AMPK signaling (a central energy sensor), insulin resistance, and longevity regulation—further underscores ZSD's potential to recalibrate systemic energy homeostasis. Notably, these mechanistic insights align with emerging therapeutic paradigms that emphasize polypharmacology in metabolic disorders, such as dual GLP-1/GIP receptor agonists and mitochondria-targeted antioxidants, thereby highlighting ZSD's translational relevance beyond its traditional use.

5. Conclusion

This study indicates that Zisheng Decoction (ZSD) has therapeutic effects on diabetic gastroparesis based on multi-components (such as kadsurenone), multi-signals (such as GCK, PPARG, INSR), and multi-paths (such as AMPK signaling, insulin resistance, galactose metabolism). This study provides a mechanistic explanation for how ZSD works in diabetic gastroparesis, and lays a hypothesis-driven basis for further experiments, such as in vitro functional assays, diabetic gastroparesis animal models, targeted metabolomic profiling, etc.

Information Accessibility Statement

All data analyzed throughout this research are available from the corresponding author given a justifiable request.

Conflict of Interest

All authors have agreed on releasing this manuscript. The authors declare no conflicts of interest.

Author Contributions

Dai-hui Li and Yao-wei Ma contributed equally to this work. Dai-hui Li and Yao-wei Ma were responsible for the literature review and manuscript drafting. Jin Li and Zhi-nan Cheng participated in the manuscript revision and reference verification.Peng-geng Shi contributed to figure preparation and data visualization. Xia Chen and Huan-tian Cui conceived the idea, supervised the project, and revised the final manuscript. All authors read and approved the final version of the manuscript.

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