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Network Pharmacology-Based Investigation of the Mechanism by Which Sijunzi Decoction Modulates Microglial Activation and Improves Diabetic Cognitive Impairment

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Abstract: Diabetic cognitive impairment (DCI) is a chronic complication of type 2 diabetes mellitus (T2DM) in which persistent neuroinflammation driven by microglial activation plays a central pathogenic role. Sijunzi decoction (SJZD), a classical formula composed of *Ginseng Radix et Rhizoma* (Renshen), *Atractylodis Macrocephalae Rhizoma* (Baizhu), Poria (Fuling) and *Glycyrrhizae Radix et Rhizoma Praeparata cum Melle* (Gancao), has demonstrated cognition-improving activity in diabetic models, yet its molecular mechanism remains unclear. Using a fully reproducible network-pharmacology pipeline, we retrieved 136 active compounds of the four component herbs from TCMSP (oral bioavailability ≥ 30%, drug-likeness ≥ 0.18) and mapped them to 413 human protein targets via UniProt. Disease targets were obtained from the Open Targets platform: 2184 targets for cognitive impairment / Alzheimer disease and 1500 for T2DM. The intersection of SJZD targets with the cognitive-impairment gene set yielded 71 putative DCI targets. A STRING protein–protein interaction network (confidence ≥ 0.40) of these targets contained 71 nodes and 280 edges (density 0.113, 5 connected components); topology analysis identified GSK3B, CTNNB1, HIF1A, CREB1, CAV1, SLC2A4, BACE1, NOS3 and JAK2 as core hub genes. Enrichr-based Gene Ontology and KEGG analysis showed that these targets were significantly enriched in adenylate-cyclase-activating adrenergic receptor signaling, G-protein-coupled receptor signaling, the insulin resistance pathway (hsa04931), neuroactive ligand–receptor interaction (hsa04080), calcium signaling (hsa04020), the cholinergic synapse and the "neuroinflammation and glutamatergic signaling" WikiPathway. These results indicate that SJZD ameliorates DCI by simultaneously regulating insulin resistance, neurotransmission and neuroinflammation, processes intimately linked to microglial activation, thereby providing a mechanistic rationale and candidate targets for subsequent experimental validation.

Keywords: Sijunzi decoction; Diabetic cognitive impairment; Network pharmacology; Microglia; Insulin resistance; Neuroinflammation

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1. Introduction

Type 2 diabetes mellitus (T2DM) can injure the central nervous system and give rise to mild cognitive impairment (MCI), a condition that manifests as a decline in learning and memory and that may progress irreversibly to dementia if

left untreated [1].

Developing agents that suppress microglial activation and neuroinflammation is therefore a rational strategy for preventing DCI.

Sijunzi decoction (SJZD) originates from the Song-dynasty *Taiping Huimin Heji Jufang* and consists of Renshen (*Panax ginseng*), Baizhu (*Atractylodes macrocephala*), Fuling (*Poria cocos*) and honey-processed Gancao (*Glycyrrhiza uralensis*). Its principal bioactive constituents—ginsenosides, sesquiterpene lactones, triterpenoids and flavonoids, are orally bioavailable and cross the blood–brain barrier. We previously showed that SJZD improved cognition and reduced hippocampal Aβ/tau and cytokines in T2DM mice, an effect causally linked to inflammation suppression [4]; however, whether it acts through regulation of microglial activation remains unclear. Because SJZD acts through multiple components, targets and pathways, a network-pharmacology strategy is well suited to dissecting its mechanism [2].

Present study applied a transparent, fully reproducible network-pharmacology and bioinformatic pipeline to (i) identify the active compounds of the four SJZD herbs and their human protein targets, (ii) define the gene set relevant to DCI, (iii) construct a compound–target network and a protein–protein interaction (PPI) network to extract core hub genes, and (iv) perform Gene Ontology (GO) and KEGG pathway enrichment to reveal the molecular mechanisms, particularly those linked to microglial activation—through which SJZD may ameliorate DCI.

2. Materials and methods

2.1. Collection of DCI disease targets

Because DCI is not a single ontological entity, we constructed a disease-target set by querying the Open Targets Platform GraphQL API (https://platform.opentargets.org) [8]. Three disease entities were used: “Cognitive impairment” (HP_0100543), “Alzheimer disease” (MONDO_0004975) and “type 2 diabetes mellitus” (MONDO_0005148).

2.2. Intersection network

The SJZD drug-target set was intersected with the cognitive disease set to yield putative DCI action targets of SJZD.

3. Results

3.1. Active compounds of SJZD

After applying the OB ≥ 30% and DL ≥ 0.18 filters, a total of 136 active compounds were retained across the four herbs: Renshen 22, Baizhu 7, Fuling 15 and Gancao 92 (the comparatively large number for Gancao reflects its rich flavonoid and triterpenoid content). Representative high-OB compounds included Celabenzine, Inermin and kaempferol (Renshen), 14-acetyl-12-senecioyl-atractylentriol and α-amyrin (Baizhu), dehydroeburicoic acid and trametenolic acid (Fuling), and Glycyrol, Licochalcone B, shinpterocarpin and licopyranocoumarin (Gancao).

3.2. Drug targets and disease targets

Mapping the herb targets to gene symbols via UniProt yielded 413 unique human gene targets for SJZD. The Open Targets query returned 2184 cognitive targets (cognitive impairment + Alzheimer disease) and 1500 T2DM targets; their intersection produced a 318-gene stringent diabetic-cognitive core set. The primary analysis used the broader cognitive set, which captures both the dementia end of the DCI spectrum and the early MCI stage.

3.3. Intersection of SJZD and DCI targets

Intersecting the 413 SJZD targets with the 2 184 cognitive targets yielded 71 putative DCI action targets (**Figure 1**). Of these, 11 were also present in the strict diabetes ∩ cognitive set, confirming diabetic relevance for a substantial fraction of the intersection. The compound–target network (**Figure 2**) contained 135 active compounds and 71 target genes joined by

5 936 edges; the targets most frequently hit across herbs included *SCN5A, GABRA1, MAOA, BCHE, CHRM1, CHRM2, CHRM3, CTSD, ADRA1B* and *SLC6A2*, reflecting the strong neuromodulatory (cholinergic, adrenergic, GABAergic and monoaminergic) signature of the formula.

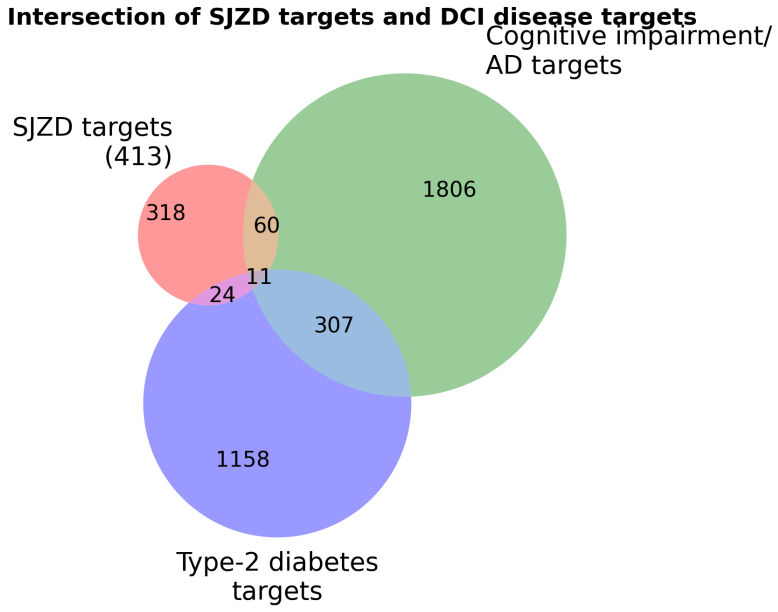

Figure 1. Venn diagram of the intersection among SJZD drug targets (413 genes), cognitive-impairment/Alzheimer disease targets (2 184) and type-2-diabetes targets (1 500) retrieved from the Open Targets platform. The 71-gene SJZD ∩ cognitive set defines the putative DCI action targets.

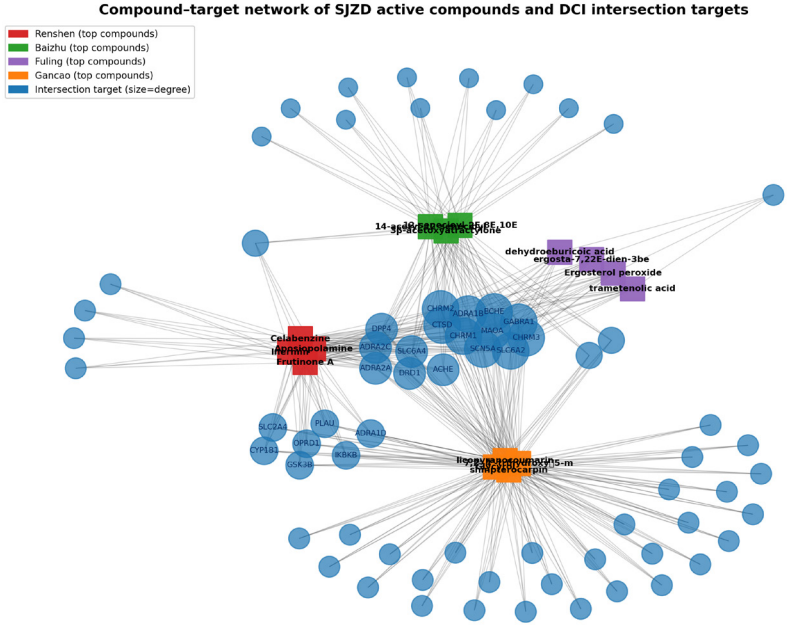

Figure 2. Compound–target network of SJZD active compounds and the 71 DCI intersection targets. Squares are representative top-OB compounds coloured by herb (red, Renshen; green, Baizhu; purple, Fuling; orange, Gancao); circles are intersection targets, sized by degree.

3.4. PPI network and core hub genes

The STRING network of the 71 intersection targets (**Figure 3)** contained 71 nodes and 280 edges, with a network density of 0.113 and 5 connected components. Degree-based topology identified GSK3B (24), CTNNB1 (23), HIF1A (21), CREB1 (19), CAV1 (18), SLC2A4 (16), PPARD (15), EP300 (15), ESR2 (14), DRD1 (14), APOB (13) and NOS3 (13) as the top-12 hub genes (**Figure 4**). Betweenness centrality ranked CAV1, CTNNB1 and GSK3B highest, underscoring their bridging role within the network.

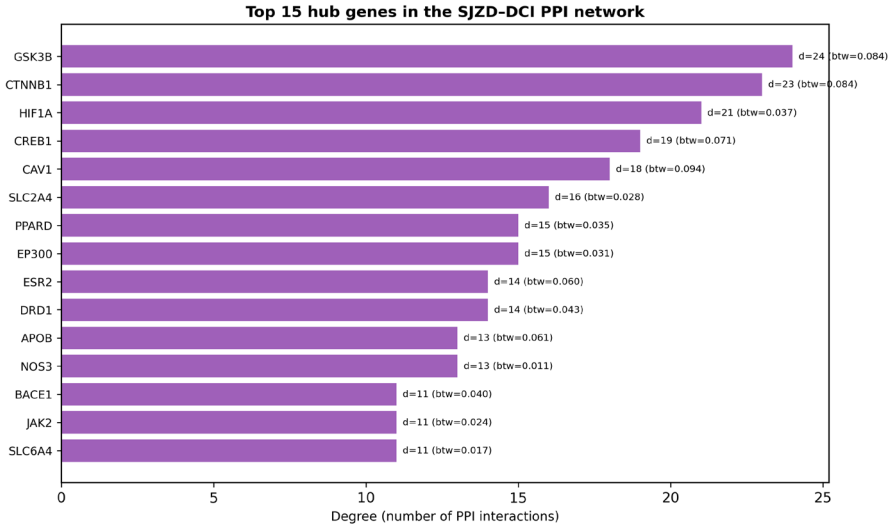

Figure 3. STRING protein–protein interaction network of the 71 DCI intersection targets (confidence ≥ 0.40). Red nodes denote the top-12 hub genes identified by degree centrality.

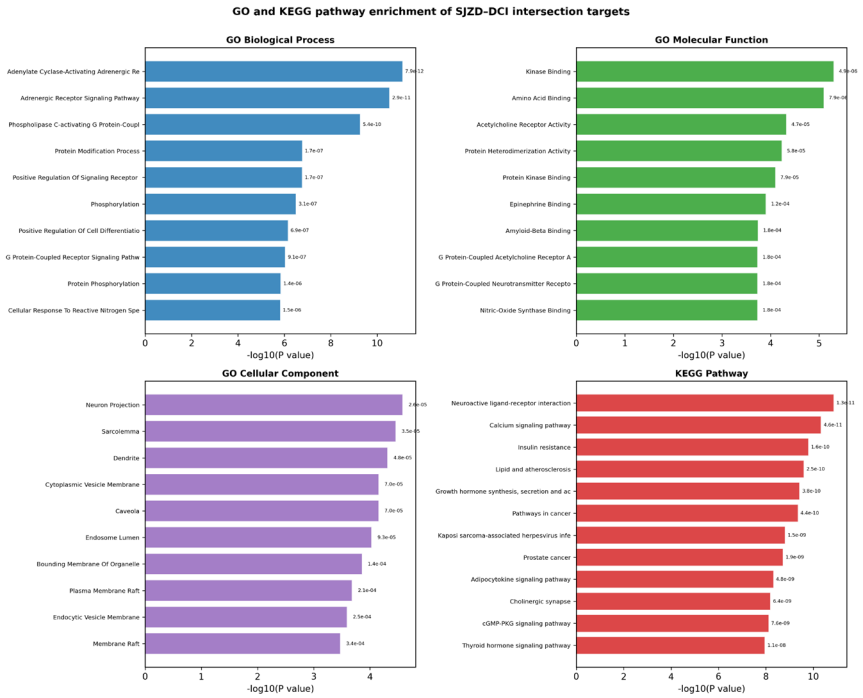

Figure 4. Top-15 hub genes in the SJZD–DCI PPI network ranked by degree, with betweenness centrality annotated.

3.5. GO enrichment

Enrichment returned 1 277 BP (594 significant), 217 MF (109 significant) and 127 CC (62 significant) terms ($p < 0.05$).

Table 1. Summary of network-pharmacology parameters and key results for the SJZD–DCI study

Metric	**Value**
Active compounds (OB ≥ 30%, DL ≥ 0.18)	136 (Renshen 22, Baizhu 7, Fuling 15, Gancao 92)
SJZD drug targets (gene symbols)	413
Cognitive impairment + AD disease targets	2 184
Type-2-diabetes disease targets	1 500
Strict cognitive ∩ diabetes core set	318
SJZD ∩ cognitive intersection (analysed)	**71**
Compound–target network edges	5 936
PPI nodes / edges	71 / 280
PPI density / components	0.113 / 5
Top hub genes (degree)	GSK3B(24), CTNNB1(23), HIF1A(21), CREB1(19), CAV1(18), SLC2A4(16)
Significant GO BP / MF / CC terms ($p < 0.05$)	594 / 109 / 62
Significant KEGG / WikiPathway terms ($p < 0.05$)	154 / 278
Top KEGG pathways	Neuroactive ligand–receptor interaction; Calcium signalling; **Insulin resistance** (hsa04931); Lipid and atherosclerosis; Cholinergic synapse
Top WikiPathway	Neuroinflammation and glutamatergic signalling (WP5083)

4. Discussion

This study used a reproducible, database-driven network-pharmacology workflow to map the mechanism by which SJZD may ameliorate diabetic cognitive impairment. The 71-gene intersection, the topology of the STRING network and the convergent enrichment results point to three interlocking biological axes: insulin resistance, neurotransmission and neuroinflammation, all of which are mechanistically tied to microglial activation, the central pathogenic process proposed in this sthdy[11].

5. Conclusion

Using a transparent and reproducible network-pharmacology pipeline, we identified 136 active compounds and 413 targets of SJZD, of which 71 converged with DCI-related genes. PPI topology and enrichment analysis revealed that SJZD is predicted to ameliorate diabetic cognitive impairment principally through the insulin-resistance, neuroactive-ligand–receptor, calcium and cholinergic-synapse pathways, with direct convergence on the neuroinflammation–glutamatergic signaling axis. The core hub genes, GSK3B, CTNNB1, HIF1A, CREB1, CAV1, SLC2A4 and BACE1, provide a prioritized target list for experimental validation of the hypothesis that SJZD improves cognitive function by suppressing microglial activation and neuroinflammation.

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Disclosure statement

The author declares no conflict of interest.

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