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Mechanism of *Ilex cornuta* Leaves in Diabetes Mellitus and its Cardiovascular Complications: a network pharmacology and molecular docking study

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Abstract: This study employed network pharmacology and molecular docking to investigate the key components and mechanisms of Ilex cornuta leaves (LCL) in treating diabetes mellitus (DM) and its cardiovascular complications. Nine active ingredients—including quercetin, kaempferol and β-sitosterol—were identified via the TCMSP database. Cross-referencing with DM-related targets from GeneCards yielded 144 common targets, of which 16 (notably AKT1, TNF and IL6) were defined as core targets. GO and KEGG analyses indicated that LCL may improve insulin resistance, suppress inflammation and reduce oxidative stress by modulating PI3K-Akt, MAPK and AGE-RAGE signaling. Molecular docking confirmed strong binding of quercetin to all ten top core targets (binding energies < -6.6 kcal/mol). The results reveal a multi-component, multi-target, multi-pathway mode of action and provide a theoretical basis for LCL in treating DM and its cardiovascular complications.

Key Words: Ilex cornuta leaves; Diabetes; Cardiovascular complications; Network pharmacology; Molecular docking

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1. Introduction

Diabetes mellitus (DM) is a globally prevalent chronic metabolic disorder and a major public health challenge[1-2]. DM patients face an elevated lifetime risk of cardiovascular complications—including cardiovascular disease, chronic kidney disease, retinopathy and peripheral neuropathy[3-6],which are leading causes of mortality, disability and economic burden[7]. Developing cost-effective therapies that delay or prevent these complications is therefore a core priority in modern medical research.

Ilex cornuta leaves (LCL), an evergreen species of the Aquifoliaceae family widely cultivated in southern China[8], have traditionally been used to clear heat, nourish Yin and treat hypertension and related symptoms[9]. Their young leaves are also consumed as ‘kuding’ tea. Modern pharmacological studies have demonstrated antioxidant[10], anti-inflammatory[11] and anti-adipogenic[12] activities, and LCL has been incorporated into several patented hypoglycemic compound formulations[13], suggesting a role in regulating glucose metabolism. However, no systematic study of its hypoglycemic mechanism has been reported. The present study therefore uses network pharmacology and molecular docking to

systematically explore the potential mechanisms of LCL in treating DM and its cardiovascular complications, aiming to provide a theoretical foundation for its application as a novel therapeutic strategy.

2. Materials and Methods

2.1. Screening the main components of LCL

Chemical components of LCL were retrieved from the TCMSP database [14] and screened by ADME criteria (oral bioavailability OB ≥ 30%, drug-likeness DL ≥ 0.18)[15], with supplementation from CNKI, Wanfang Data and PubMed.

2.2. Screen the target sites of the main components of LCL

Component targets were obtained from TCMSP. For components lacking annotated targets, SMILES strings retrieved via HERB and PubChem were submitted to SwissTargetPrediction[16] (Homo sapiens, probability > 0.1). All target lists were standardized and deduplicated in UniProt (reviewed, Homo sapiens).

2.3. Screening for potential core targets of DM

DM-related targets were retrieved from the GeneCards, OMIM and DrugBank databases using 'Diabetes Mellitus' as the keyword, retaining targets with a relevance score ≥ 2× the median. Lists were standardized in UniProt and deduplicated.

2.4. Construct the interaction network of LCL and DM core intersection targets

Intersection targets between LCL and DM were obtained via the jvenn platform [17]. The intersection was imported into Cytoscape 3.10.2 for topological analysis, with core targets defined as those with a degree value > 2× the median. A protein–protein interaction (PPI) network of the core targets was constructed in STRING 12.0[18] (Homo sapiens).

2.5. Core target GO enrichment analysis and KEGG pathway analysis

GO enrichment analysis (BP, CC and MF; Homo sapiens; min overlap = 3, min enrichment = 1.5, $P < 0.01$) was performed using Metascape[19]. KEGG pathway enrichment was performed using the KEGG platform[20].

2.6. Molecular docking

Molecular docking was performed with AutoDock Vina. Target protein 3D structures were retrieved from the RCSB PDB and prepared in PyMol 3.0. 2D ligand structures from PubChem were energy-minimized in Chem3D 20.0. Docking grids covered the active sites; 20 simulations per pair were run with the Lamarckian genetic algorithm (LGA) using default parameters. Conformations with the lowest binding energy were retained, and binding modes, interaction types and key residues were analyzed.

3. Results and Analyses

3.1. Main components and Target Sites of LCL

Based on ADME screening, 9 major active components of LCL were identified from 94 candidates: ursolic acid (Mairin), β-sitosterol, kaempferol, (+)-catechin, (-)-catechin gallate, quercetin, amyrin palmitate, ilexgenin B and taraxerol. A total of 221 verified Homo sapiens targets were retrieved. Network analysis (Figure 1) identified quercetin (LCL6) as the most central component, with the highest degree value, the highest betweenness centrality (0.7719) and closeness centrality (0.6074), and the lowest average shortest path length (1.64629); kaempferol and β-sitosterol were the next most central.

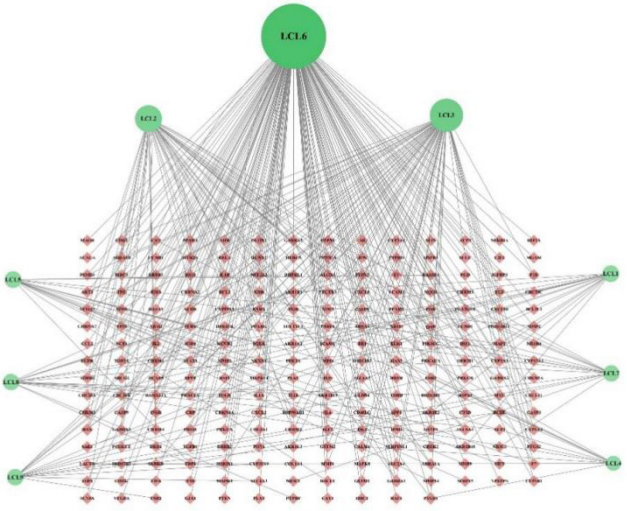

Figure 1. LCL main component-target interaction network

3.2. Construction of the PPI network of LCL and DM core therapeutic targets

A total of 2,451 verified DM-related Homo sapiens protein targets were obtained after retaining those with relevance scores ≥ 2× the median. Venn analysis with the LCL component targets yielded 144 intersection targets (**Figure 2**). Topological analysis in Cytoscape 3.10.2 (degree > 2× the median of 83.0) identified 16 core therapeutic targets (**Figure 3**). The STRING 12.0 PPI network of these 16 targets contained 16 nodes and 120 edges (average node degree = 15; expected edges = 93; PPI enrichment P = 0.00113), confirming significant interconnectivity (**Figure 4**).

Figure 2. Venn analysis of potential targets for the treatment of DM with LCL

Figure 3. PPI network of potential targets for treating DM with LCL

Note: The color ranges from light to dark to represent the degree values from small to large, with the maximum set at 83.0

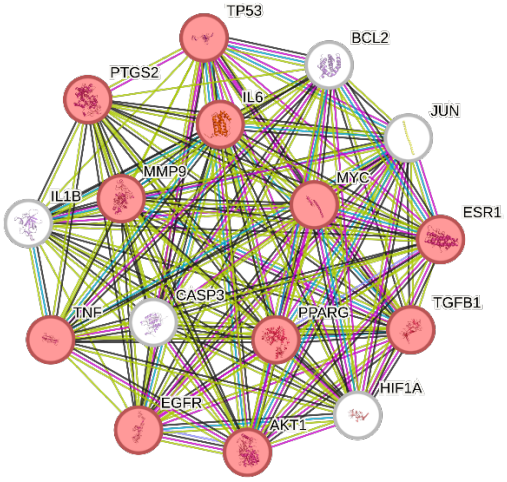

Figure 4. PPI network of the core targets for treating DM with LCL

3.3. Results of GO enrichment analysis of core targets

GO enrichment of the 16 core targets yielded 34 MF terms (mainly DNA-binding transcription factor activity and RNA polymerase II-specific transcription activator activity), 456 BP terms (mainly regulation of miRNA transcription and ncRNA metabolic processes) and 9 CC terms (mainly transcription regulator complexes, euchromatin and membrane microdomains). The top 10 terms in each category are visualized in **Figure 5**, with bubble size positively correlated with enriched gene count and darker color indicating smaller *P* value[21].

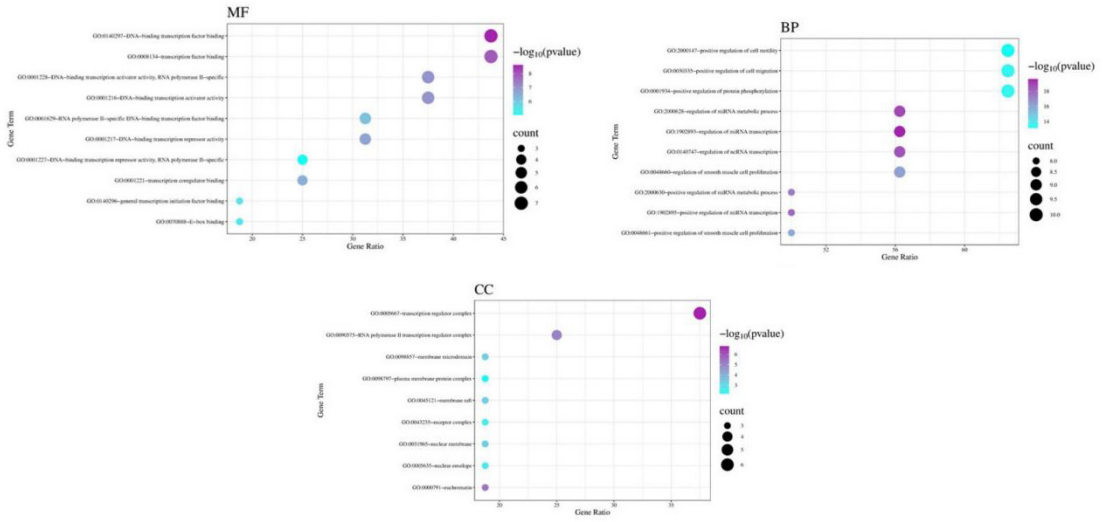

Figure 5. GO enrichment analysis of the core targets for LCL treatment of DM

3.4. KEGG pathway analysis of the core target

KEGG analysis yielded 180 pathways, of which 15 DM-related pathways were retained after literature review—including MAPK (hsa04010), PI3K-Akt (hsa04151), AGE-RAGE in diabetic complications (hsa04933), non-alcoholic fatty liver disease (hsa04932), lipid and atherosclerosis (hsa05417), apoptosis (hsa04210) and endocrine resistance (hsa01522). These spanned the four KEGG categories of Environmental Information Processing, Cellular Processes, Organismal Systems and Human Diseases (**Figure 6A**), implicating multiple mechanisms in DM and its cardiovascular complications. Venn analysis of six DM-related pathways—covering insulin signaling and glucose metabolism (PI3K-Akt), oxidative stress and inflammation (AGE-RAGE, MAPK), lipid metabolism and atherosclerosis, hepatic insulin resistance (NAFLD) and β-cell apoptosis—identified AKT1 as the key shared target (**Figure 6B**), with the PI3K-Akt pathway emerging as the core pathway in DM pathology (**Figure 6C**).

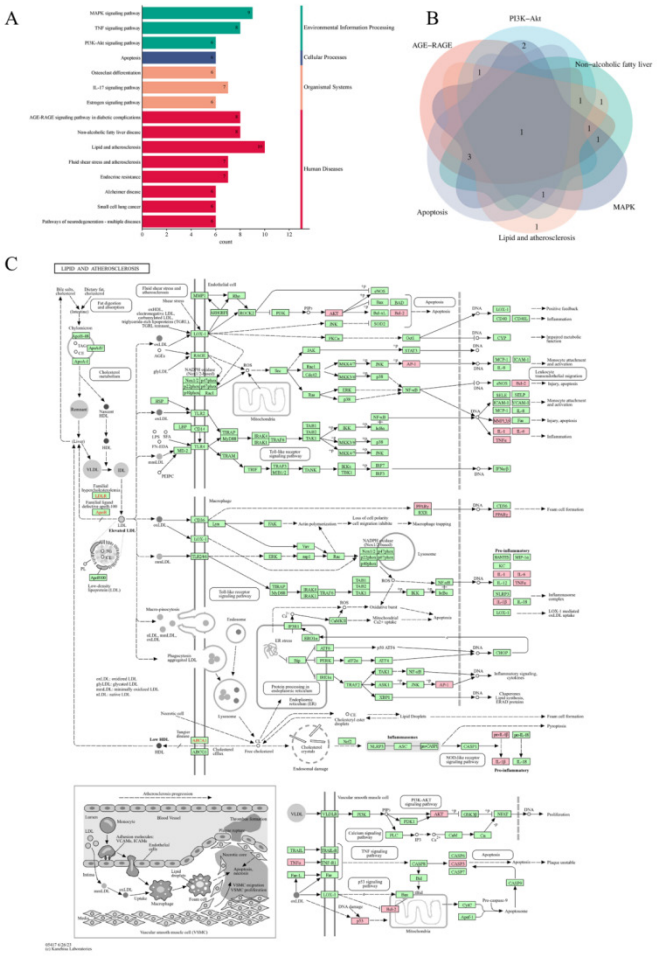

Figure 6. KEGG pathway analysis of LCL for treating the core target of DM

Note: A. Analysis results of 15 related pathways; B. Venn analysis results of 6 closely related pathways; C. Lipid and atherosclerosis pathway signaling pathway representation

3.5. Molecular docking results

To characterize the molecular interactions between quercetin (LCL6) and the top 10 core targets in the PPI network, AutoDock Vina was used for docking simulations (**Figure 7**). Binding energies below -6.0 kcal/mol typically indicate stable conformations. All ten complexes showed strong binding (all < -6.6 kcal/mol), with the strongest affinities for PTGS2 (-9.3 kcal/mol) and TNF (-9.0 kcal/mol), followed by AKT1 (-7.5), IL6 and EGFR (-7.3), TP53 (-7.2), and IL1B and CASP3 (-6.6). The dominant interactions were hydrogen bonds, supporting quercetin as a robust multi-target ligand.

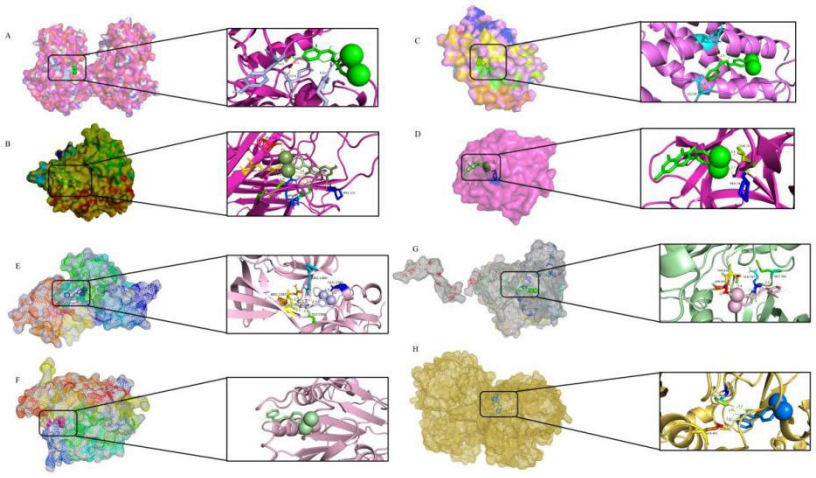

Figure 7. Quercetin docking results with key target molecules

4. Discussion

Network pharmacology analysis revealed that the main active components of LCL treat DM and its cardiovascular complications through multiple targets and pathways, with the PI3K-Akt pathway as the central mechanism. Quercetin, exhibiting the highest centrality, is likely the principal active ingredient; it may enhance insulin sensitivity and glucose metabolism by activating PI3K-Akt via AKT1, while also preserving β-cell function. Kaempferol and β-sitosterol also showed high centrality, contributing antioxidant, anti-inflammatory and cholesterol-regulating effects, thus supporting a synergistic multi-target action. AKT1 emerged as the core target with the highest degree in the PPI network, linking PI3K-Akt to MAPK-mediated inflammatory/oxidative responses and AGE-RAGE-driven microvascular complications. LCL may attenuate tissue damage by suppressing aberrant MAPK activation and slow retinopathy, nephropathy and cardiovascular disease by reducing AGE formation or blocking RAGE. These findings suggest that LCL holds potential as a natural multi-target agent for mitigating microvascular injury and cardiovascular risk and may be valuable in combination with existing anti-diabetic drugs. However, the predicted component–target–pathway interactions require in vitro and in vivo validation, and additional active constituents remain to be characterized.

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Disclosure statement

The author declares no conflict of interest.

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