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Network Pharmacology Analysis of the Mechanism of Action of *Paederia scandens* in the Treatment of NAFLD

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Abstract

Objective: This study aimed to elucidate the mechanism of action of *Paederia scandens* in the treatment of nonalcoholic fatty liver disease (NAFLD).

Methods: The Tcmsp database was used as a search platform for main chemical components of *Paederia scandens* and screening for their target sites. NAFLD-related genes were obtained from the GeneCards and OMIM databases. Common target genes of the disease and drugs were mapped using the UniProt database, and the compound-target network of *Paederia scandens* and NAFLD was construct using the Cytoscape software. The string database was used to construct the protein interaction network to screen for core genes. Finally, the Gene Ontology functional enrichment analysis and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis were carried out using the DAVID database to elucidate the possible mechanism of action of *Paederia scandens*.

Results: Based on the analyses, 57 target genes, seven common molecules, and four signaling pathways were found to be associated with the treatment of NAFLD with *Paederia scandens*. The data suggested that the mechanism of action of *Paederia scandens* might be related to insulin resistance and oxidative stress in the pathogenesis of NAFLD and might involve genes encoding important targets, such as AKT1, IL10, CYP1A2, CYP1A1, and CYP3A4.

Conclusion: Through network pharmacology, the mechanism of action of *Paederia scandens* in the treatment of NAFLD was elucidated, and the data provide new ideas for the use of *Paederia scandens* in the treatment of metabolic disorders.

Keywords: *Paederia scandens*; NAFLD; Network pharmacology

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a clinical pathological syndrome characterized by excessive deposition of liver fat in the absence of excessive drinking and other pathogenic factors. NAFLD is the most common acquired metabolic stress liver disease. Damage, inflammation, and fibrosis of liver cells are common in the pathological process, which may lead to the development of clinical diseases such as nonalcoholic steatohepatitis, cirrhosis, and liver cell carcinoma. Moreover, NAFLD increases the prevalence of cardiovascular disease, obesity, hypertension, hyperlipidemia, and other diseases. Based on research reports, with the change in the diet and lifestyle, the prevalence of NAFLD in China steadily increases, and the disease becomes younger [1].

According to the Chinese Materia Medica, *Paederia scandens* (Chinese fevervine), which belongs to Rubiaceae, has a flat nature and a sweet and sour flavor, which means tonic and astringent effects. The herb is used as the whole grass and roots. Modern pharmacological research has revealed that the central nervous toxicity of dimethyl disulfide, found in P. scandens, can play an analgesic role and be used to treat rheumatoid arthralgia [2]. In addition, the iridoid terpenoid extract of *Paederia scandens* exerts certain hypoglycemic effects [3], likely due to delaying the damage to pancreatic islets, caused by endoplasmic reticulum stress, by inhibiting the activity of NF-κB [4]. Moreover, iridoids from *Paederia scandens* can significantly reduce the levels of glutamic-pyruvic transaminase and glutamic-oxaloacetic transaminase to protect the liver [5]. In recent years, the clinical application research of *Paederia scandens* has been gradually expanding, but its application in the treatment of liver diseases has not been sufficiently explored.

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In this study, the mechanism of action of *Paederia scandens* in the treatment of NAFLD was explored through network pharmacology to provide theoretical support for the application and expansion of the use of *Paederia scandens* in the treatment of liver diseases.

2. Materials and methods

2.1 Databases and software

The following databases and software were used in this study: TCMSP (http://tcmsp-w.com/tcmsp.php), UniProt (http://www.Uniprot.org/), GeneCards (https://www.genecards.org/), Online Mendelian Inheritance in Man (OMIM; http://www.omim.org/), DAVID (https//david.ncifcrf.gov/home.jsp), Kyoto Encyclopedia of Genes and Genomes (KEGG; http://www.genome.jp/kegg/), STRING (https://string-db.org/), Cytoscape 3.7.1, the R language software (https://www.r-project.org/), and Bioconductor (https://www.bioconductor.org/).

2.2 Database screening for chemical pharmaceutical ingredients

In the Traditional Chinese Medicine comprehensive database (TCMSP), "*Paederia scandens*" was used as the search term. The main chemical components were screened using as the filter conditions, oral utilization (OB) greater than 30% and the drug-like (DL) value greater than 0.18.

2.3 Target prediction for active chemical ingredients

The TCMSP database was used to screen for the targets of the active chemical components of *Paederia scandens*, and the names of the targets that met the screening criteria were converted to the UniProt ID format.

2.4 Acquisition of NAFLD-related target genes

In the GeneCards and OMIM databases, "NAFLD" was used as the search term to search for the target genes related to nonalcoholic fatty liver. Subsequently, these genes were matched with the predicted target genes of the active molecules of *Paederia scandens* to identify common target genes and determine the potential mechanism of action of the active components of P. scandens in the prevention of NAFLD.

2.5 Network construction and analysis

The common target genes that may affect NAFLD were analyzed using the String database to establish a protein–protein interaction (PPI) network. All genes whose degree in the correlation relationship was more than 4 were selected as core genes.

2.6 Analysis of biological functions and pathways

The common target genes of *Paederia scandens* and NAFLD were analyzed for the enrichment of Gene Ontology (Go) biological function and KEGG pathways.

2.7 Composition and target network construction

The active components of *Paederia scandens* and the targets that can be used to treat NAFLD were introduced into the Cytoscape software to construct a network of active components and targets.

3. Results

3.1 Active chemical components of *Paederia scandens*

Eleven main active compounds in *Paederia scandens* were identified through the database search as follows: paederosidic acid methyl ester, pelargonidin, kaempferol, acacetin, quercetin, delphinidin, linarin, poriferast-5-en-3-beta-ol, sitosterol, beta-sitosterol, and paederoside, as shown in Table 1.

3.2 Overlapping gene targets between *Paederia scandens* and NAFLD

A total of 931 gene targets of the 11 active chemical components of *Paederia scandens* were obtained from TCMSP. After these were matched with 88 NAFLD-related genes, identified in the GeneCards and OMIM databases, the following 57 common gene targets were obtained: *HMOX1*, *AHSA1*, *MMP2*, *PON1*, *SERPINE1*, *CCL2*, *COL1A1*, *HSPB1*, *IL1A*, *IL1B*, *TP63*, *ICAM1*, *SOD1*, *PPARG*, *BAX*, *VCAM1*, *BIRC5*, *INSR*, *COL3A1*, *FASN*, *ADRB2*, *CXCL8*, *CASP3*, *GSTM1*, *NOS2*, *F3*, *NR1I2*, *CYP3A4*, *CAV1*, *CYP1A2*, *SLPI*, *CASP8*, *PARP1*, *PTGS2*, *FASLG*, *NR1I3*, *JUN*, *MMP9*, *PLAU*, *THBD*, *CYP1A1*, *MAPK8*, *NFE2L2*, *BCL2*, *GSTP1*, *RELA*, *CDKN1A*, *PPARA*, *IL6*, *ESR1*, *IL10*, *RXRA*, *IKBKB*, *HIF1A*, *AKT1*, *VEGFA*, *ACACA*. The details are shown in Figure 1.

3.3 Construction and analysis of the core network

After identifying the 57 overlapping genes, genes with a degree greater than 4 were selected as the core genes. All target genes were input into the string database to determine the relationship between the active molecules of *Paederia scandens* and NAFLD-related targets to construct a target interaction

network. PPI analysis produced 25 core gene nodes and 82 link edges. The more connected the edges between two nodes are, the greater the degree of correlation is; the average degree of nodes was 6.56, as shown in Figures 2 and 3.

3.4 Enrichment analysis

The Bioconductor database, combined with the R language software, was used to predict the enrichment of GO functional terms and KEGG signaling pathways for the 57 targets for the treatment of NAFLD.

GO function enrichment analysis. The 57 genes relevant to NAFLD were input into the David database for go biological function enrichment analysis. The threshold was set at $P < 0.05$, resulting in 104 entries from the common enrichment set, and the top 20 plots with significant differences were selected, as shown in Figure 4.

KEGG pathway enrichment analysis. After screening, four signaling pathways were obtained, which were related to endocrinic resistance, metabolism of xenobiotics by cytochrome P450, EGFR tyrosine kinase inhibitor resistance, and drug metabolism by cytochrome P450, as shown in Figure 5.

3.5 Construction of the active component network

Figure 6 shows the network of active components of *Paederia scandens* and NAFLD targets, obtained

Table 1 Main active chemical constituents of *Paederia scandens*

Mol ID	Chemical constituent	OB (%)	DL
MOL010606	Paederosidic acid methyl ester	67.65	0.2
MOL001004	Pelargonidin	37.99	0.21
MOL000422	Kaempferol	41.88	0.24
MOL001689	Acacetin	34.97	0.24
MOL000098	Quercetin	46.43	0.28
MOL004798	Delphinidin	40.63	0.28
MOL001790	Linarin	39.84	0.71
MOL001771	Poriferast-5-en-3-beta-ol	36.91	0.75
MOL000359	Sitosterol	36.91	0.75
MOL000358	Beta-sitosterol	36.91	0.75
MOL010603	Paederoside	57.19	0.76

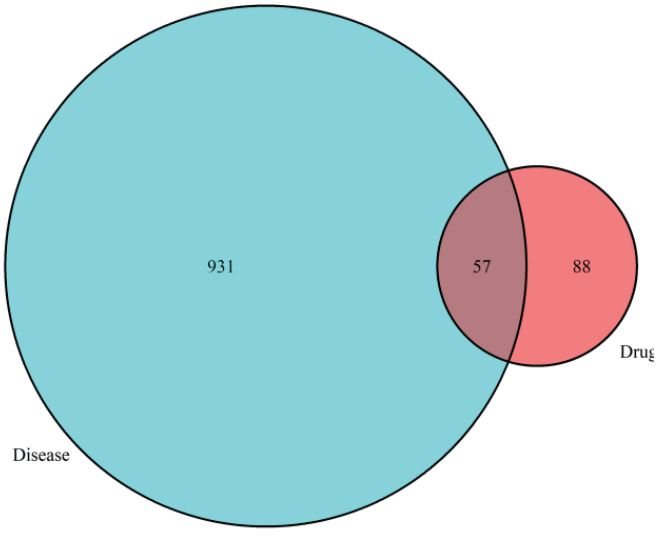

Fig. 1 Overlapping gene targets between *Paederia scandens* and NAFLD

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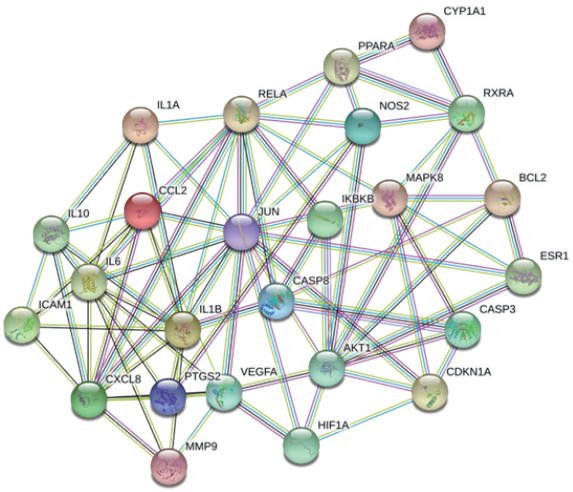

Fig. 2 Protein interaction network of *Paederia scandens* and NAFLD

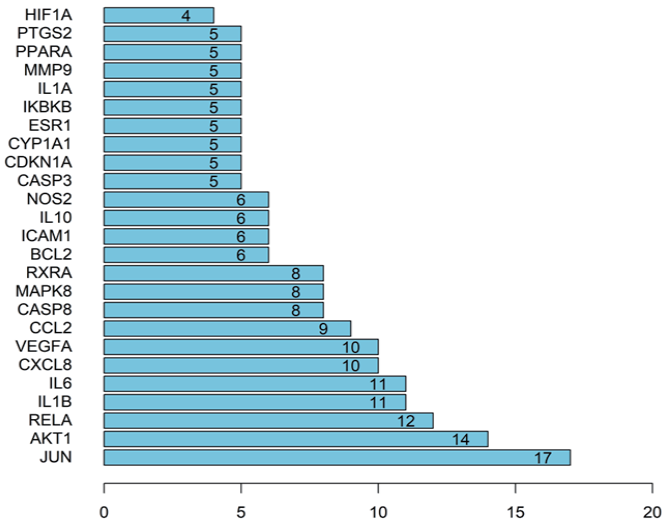

Fig 3 Gene degrees in the protein interaction network

Fig 4 Bubble diagram of GO functional enrichment analysis

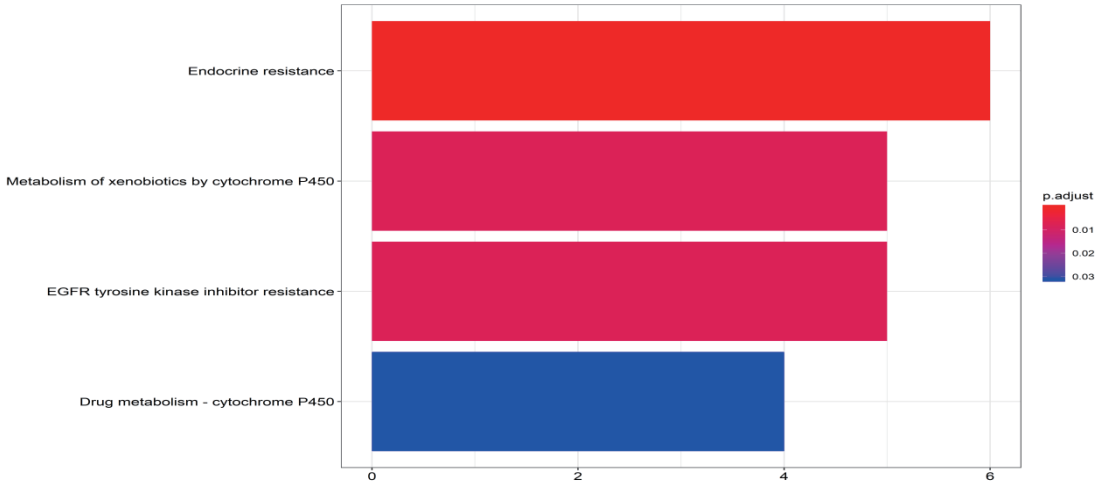

Fig. 5 Histogram of KEGG signaling pathway enrichment analysis

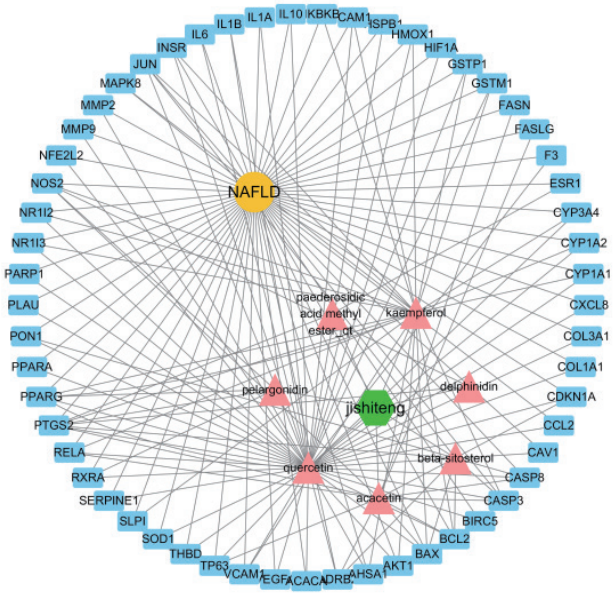

Fig 6 Disease–drug ingredient–target–signaling pathway network

Triangle nodes represent the active components of *Paederia scandens*; elliptical node represents the NAFLD disease; square nodes represent the overlapping targets; and sidelines represent the correlation between the active component and potential target.

using the Cytoscape software.

4. Discussion

In traditional Chinese medicine, the common diagnoses of NAFLD are "liver fixity", "hypochondriac pain", and "liver addiction", among others. Clinically, no distinctive symptoms can be defined, but abdominal obesity, fatigue, accompanied by hypochondriac pain and discomfort, epigastric fullness, a light tongue, white and greasy fur, and a smooth pulse may be observed in different patients [6].

As a common traditional Chinese medicine, combining characteristics of both medicine and food, *Paederia scandens* can be taken together with glutinous rice to treat infantile malnutrition and to relieve heartburn, belch, fullness, epigastric discomfort or pain, and other symptoms [7]. The herb also plays a role in eliminating food accumulation. When *Paederia scandens* extract is injected into the joint cavity, its iridoid components can work as anti-inflammatory and analgesic agents to reduce inflammation [8, 9]. After *Paederia scandens* is

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boiled, it can be used to promote the recovery of gastrointestinal peristalsis after cesarean section [10]. For the treatment of liver disease, Huang et al. [11] used the Hua Xian Ruan Gan prescription of *Paederia scandens*, combined with a liver disease treatment instrument, to treat patients with chronic hepatitis B. The results showed that the degree of liver fibrosis was lower than that in patients who did not receive the traditional Chinese medicine, and the liver function significantly improved. Thus, the data suggest that *Paederia scandens* exerts certain anti-inflammatory effects and may treat diseases of the digestive system.

In this study, the main active molecules of *Paederia scandens* that may be involved in the treatment of NAFLD were found to be pelargonidin, paederosidic acid methyl ester, acacetin, kaempferol, delphinidin, quercetin, and β-sitosterol. AKT1, IL10, CYP1A2, CYP1A1, and CYP3A4 were found to be the main targets in signaling pathways. Among them, AKT1 is associated with the endocrine resistance pathway; AKT1 and IL10 are associated with the resistance pathway of epidermal growth factor receptor tyrosine kinase inhibitor; metabolism of exogenous substances by cytochrome P450 involves CYP1A1 and CYP1A2; and drug metabolism by cytochrome P450 involves CYP1A2 and CYP3A4.

In insulin resistance, the dynamic balance of liver fat is destroyed, and the liver ability to oxidize fatty acids is decreased, which eventually leads to the development of NAFLD, exhibited as fat deposition in hepatocytes and liver steatosis [12]. Akt1 is known to be a component of the downstream pathway of pi3k/p85, which is related to insulin metabolism and can regulate glucose intake and lipid metabolism. Overexpression of AKT1 can lead to the increase of fasting or non-fasting blood glucose and induce insulin resistance [13]. CYP1A2, CYP1A1, and CYP3A4 are known to be involved in drug metabolism in the liver. These enzymes can participate in NADPH-dependent electron transport pathways to perform various oxidation reactions [14]. In the pathogenesis of NAFLD, oxidative stress can lead to the progression of steatosis to steatohepatitis, whereas oxidative stress and lipid peroxidation can lead to inflammation, necrosis, and fibrosis of the fatty liver [12]. It was shown that NAFLD rats had hyperglycemia and hyperlipidemia, increased levels of inflammatory factors, and decreased levels of anti-inflammatory factors [15]. Studies have shown that IL-10 is an important anti-inflammatory cytokine in the human body, and its secretion level is negatively correlated with the degree of inflammation and steatosis.

In conclusion, based on the targets of NAFLD and *Paederia scandens*, the herbal medicine may be able to alleviate the phenomenon of insulin resistance by regulating the insulin downstream gene expression in the process of NAFLD onset and act on related enzymes in the oxidative stress response to slow down the progress of NAFLD. It can also regulate the release of inflammatory factors in the course of NAFLD progression to steatohepatitis or liver fibrosis, preventing further deterioration of the liver. In this study, we explored the possible target sites and related mechanisms of *Paederia scandens* in the treatment of NAFLD through network pharmacology. The findings are consistent with the possibility of clinical application of *Paederia scandens* and may provide new ideas for the treatment of NAFLD.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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