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Analysis of the Network Pharmacological Mechanism of Action of Panax Ginseng Component-Target-Pathway on Diabetic Eye Disease

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Abstract

The key targets and pathways of Panax notoginseng in treating diabetic eye disease were explored based on network pharmacology and molecular informatics methods. The chemical composition of Panax notoginseng was obtained by TCMSP database, the potential target of Panax notoginseng was predicted by Swiss Target Prediction database, the diabetic eye disease target was queried by Gene Cards database, and the intersection of Panax notoginseng component target and eye disease target was visualized by Winn Diagram. The protein-protein interaction network was constructed using STRING database, and topological parameter analysis was carried out on Cytoscape to obtain the key targets of Panax notoginseng in the treatment of eye disease. GO and KEGG analysis were carried out based on Metascape database, and GO enrichment heat map and KEGG enrichment bubble map of core targets were constructed using Weisengxin website. Eight effective chemical components of Panax notoginseng were screened out, including 147 key targets, and 1366 key targets of diabetic eye disease. Seventy-seven overlapping targets were screened out by intersection analysis. The enrichment analysis of intersection targets showed that Panax notoginseng had effects on diabetic eye disease through 16 KEGG and 58 Go-related signaling pathways. This study shows how eight active chemical components of Panax notoginseng play a role in the treatment of diabetic eye disease through nine key targets.

Keywords: Network pharmacology; Molecular informatics; Notoginseng; Diabetic eye disease

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Introduction

Diabetic ophthalmopathy is a common blinding disease commonly associated with diabetes mellitus, which has received increasing attention in recent years [1-3]. Among them, retinopathy is the most common diabetic eye disease. In the pre-disease stage, retinal blood vessels become blocked, inducing changes in the lens thus leading to vision loss. At this stage, if prevention is neglected and timely treatment is not taken, persistent high blood glucose may cause vascular proliferation, leading to retinal detachment and inducing blindness [4-12]. The number of diabetic patients is increasing in our country, in which diabetic eye disease is a common complication, its development seriously affects the quality of life and financial energy of patients. The search for effective therapeutic strategies is of utmost importance.

For the treatment of this disease, the main clinical use of cytoprotective mainly with neurological and vasoprotective agents symptomatic treatment. Nowadays, many western drugs have been proved to have a therapeutic effect on diabetic eye disease, such as Lucentis, a representative drug of anti-vascular endothelial growth factor (Vinyl Ester Glass Flake (VEGF)), which has achieved better efficacy in recent years [13-15]. However, due to the drawbacks of western drugs, such as high side effects and many adverse reactions, Chinese medicine has gradually become a new choice. Chinese medicine has many advantages in preventing diabetic complications, which are reflected in its less toxicity, fewer side effects, and the ability to "cure the disease before it occurs" [16-18]. The mutual supplementation of Chinese and Western medicines is getting more and more attention. Research has shown that most of the Chinese medicines that have the effect of activating blood circulation and removing blood stasis and protecting blood vessels also have certain hypoglycaemic effects. Panax ginseng is one of them [19]. As a medicinal herb, Panax ginseng is the dried root and rhizome of

Panax quinquefolium, a plant of the family Wujiaceae, which has the efficacy of stopping bleeding, dispersing blood, fixing pain, activating blood circulation and removing blood stasis, and is used clinically to treat bruises and injuries. And Panax notoginseng polysaccharide, the main component of Panax notoginseng, can improve diabetes-induced retinopathy by elevating GSH and NO levels and increasing iNOS (inducible nitric oxide synthase) gene expression [20,21].

In conclusion, Panax ginseng has clinical therapeutic effects on diabetic eye disease, but the molecular mechanism of Panax ginseng in diabetic eye disease has rarely been reported [22-24]. Network pharmacology, an emerging approach that integrates systems biology and polypharmacology, provides a powerful tool for understanding the complex interactions between drugs and diseases. Network pharmacology, on the other hand, spans systems biology as an interdisciplinary discipline that enables networked rather than isolated analyses of biological systems [25-29]. Network pharmacology straddles systems biology as an interdisciplinary discipline, which analyses biological systems in networks rather than in isolation. This feature matches and compares well with the complex mechanism of action of traditional Chinese medicine and has recently become a good approach for the study of Chinese medicine. The approach of network pharmacology for TCM research is to take the components, targets and diseases interrelated with each other as the sail, and build out the network with the whole and system as the anchor, which has already achieved better results. Existing studies have already shown that Panax ginseng can be effective in diabetic ophthalmopathy, and the present study explores the mechanism of action of Panax ginseng in the treatment of diabetic ophthalmopathy from the perspective of cyberpharmacology.

Experimental Section

Experimental materials and programmes

Public information and open databases: China Knowledge (https://www.cnki.net/), TCMSP online database to find the effective compound components of Panax ginseng (https://old.tcmspe.com/tcmsp.php), PubChem database for chemical information related to compound components (https://pubchem. ncbi.nlm.Nih.gov/), Swiss Target Prediction online web platform (https://old.tcmspe.com/tcmsp.php target prediction. ncbi.nlm.Nih.gov/), Swiss Target Prediction online platform (http://swiss target prediction.ch/), GeneCards Disease Database (https://www.genecards.org/), STRING (https://string-db.org/cgi/input.pl), online Venn diagrams (https://bioinfogp.Cnb.csic.es/tools/venny/), Cytoscape software (Version 3.7.2), Metascape database (https://string-db.org/cgi/input.pl), and the Venn diagrams (https://bioinfogp.Cnb.csic.es/tools/venny/). Metascape database (https://metascape.org/gp/index.html), and the Microbiology Letter Network (http://www.bioinformatics.com.cn/).

Methods

Acquisition of Panax notoginseng chemical composition and targets: The chemical composition of Panax quinquefolium was obtained through TCMSP database, and the Canonical Smiles numbers of these components were obtained by importing into Pubchem database using InChIKey. The principle of screening is to import the collected Smiles of Panax notoginseng into Swiss Target Prediction database, limit the research target to human (Homo) species, and use probability ≥ 0.08 as the threshold value for screening, and discard the components with target probability ≤ 0.08, so as to obtain the more relevant targets.

Disease target acquisition and intersection of Panax quinquefolius: Search for Diabetic eye disease in the Genecards database, and filter out the targets with a score (Score) ≥ 20 in the results obtained. The intersection of the obtained Panax ginseng targets with the disease targets was taken, and a Wayne diagram was created using an online website to visualize the intersection.

Component target network construction and analysis: Construct a network between the obtained constituent targets of Panax ginseng and the targets of diabetic eye disease. Using Panax notoginseng drug name, Panax notoginseng constituents and the intersection targets of Panax notoginseng and the disease as anchor points, Cytoscape 3.7.2 software was used to construct the "constituent-target" network.

Protein-protein interaction (PPI) network: The obtained targets at the intersection of Panax ginseng and diabetic ophthalmopathy were imported into the STRING database, with the species limited to the human species genus (Homo sapiens), and the Protein-Protein Interaction network (PPI), or PPI, of the obtained targets.

Finding core targets: The Protein-Protein Interaction (PPI) network of the target under 4.1.2.4 is exported in the format of "TSV" (lists reciprocal edges: A-B, B-A), and then imported into Cytoscape 3.7.2 software, and the CytoNGA plug-in is used to find the core target according to the following criteria BC (Betweennes), DC (Degree), CC (Closeness), EC (Eigenvector) to filter out the mean value above is called the core target.

Target enrichment analysis: The intersecting targets under 4.1.2.2 were subjected to GO bioprocess enrichment analysis and KEGG pathway enrichment analysis *via* Microbiotics database, and plotted as bubble diagram and enrichment heat map.

Results and Discussion

Panax notoginseng composition collection and target prediction

Through TCMSP database and literature search, 119 chemical components of Panax notoginseng were obtained, with OB (oral bioavailability) ≥ 30% and DL (drug-like properties) ≥ 0.18 as the criteria, several compounds were removed, and finally eight active components were obtained, as shown in Table 1. These included diethylstilbestrol (DFV), flavonoids (quercetin), ginsenoside rh2 (qinsenoside rh2), and ginsenoside f2 (qinsenoside f2). 292 potential targets of the compounds were predicted by Swiss Target Prediction database.

Prediction of disease targets

Disease targets related to diabetic eye disease were obtained

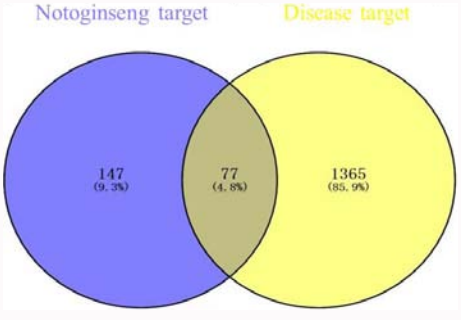

Figure 1: Panax notoginseng-diabetic eye disease of Venn diagram.

Table 1: Chemical constituents of panax notoginseng.

MOL ID	Target	DL	OB%
MOL001792	DFV	32.8	0.18
MOL001494	Mandenol	42	0.19
MOL007475	Ginsenoside f2	36.4	0.25
MOL000098	Quercetin	46.4	0.28
MOL002879	Diop	43.6	0.39
MOL005344	Ginsenoside rh2	36.3	0.56
MOL000358	Beta-sitosterol	36.9	0.75
MOL000449	Stigmasterol	43.8	0.76

as 1442 by Gene Cards database, and 77 overlapping targets were obtained by doing a Wayne's plot to take the intersection with Panax ginseng targets, see Figure 1.

Construction and analysis of the "component-target" network

The information of Panax notoginseng components and targets was imported into Cytoscape 3.7.2 software to construct the "component-target" network, see Figure 2. The results showed that, except for individual components, an active component often corresponds to more than one target, and a target often corresponds to more than one component, which is a reciprocal counterpart of each other. This phenomenon makes the fact that Panax notoginseng can produce effects on multiple targets through the action of multiple components in the treatment of diseases more plausible.

Protein-Protein Interaction (PPI) network content analysis

After observation, we found that the links between proteins were not extensive and close, and targets such as MYKL4 and CLEC14A existed in isolation in the PPI diagram, while most of the network links appeared in a few targets such as CBL and JAK1 (Figure 3). Therefore, the analysis of the core targets is particularly critical.

Table 2: Core Target.

0	Target	Degree	Eigenvector	Betweenness	Closeness
1	PPARG	20	0.32765353	506.80316	0.168776
2	CBL	20	0.41573006	439.54126	0.165975
4	PLCG1	14	0.31548992	110.81587	0.156863
5	PTGS2	14	0.19552204	215.59047	0.15873
6	KIT	12	0.26202178	73.41111	0.152672
7	NCOA3	12	0.13752878	238.84445	0.155642
8	KITLG	10	0.256281	96.03809	0.156863
9	VDR	10	0.18481682	105.922226	0.158103
10	Average	6.341463	0.10944341	68.7848713	0.134148

Finding core targets

Using CytoNCA plug-in in Cytoscape, we obtained BC, DC, CC and EC data of 41 targets, and screened those whose BC, DC, CC and EC were above the mean value, which were called core targets, and we obtained a total of 9 core targets. The following targets were obtained by screening, see Table 2.

Enrichment analysis

The intersecting targets under 3.2 were calculated and analyzed using the DAVID online analysis platform, and the GO enrichment analysis yielded 20 entries of Biological Process (BP), which mainly involved response to hormone; pathways in cancer; and 20 entries

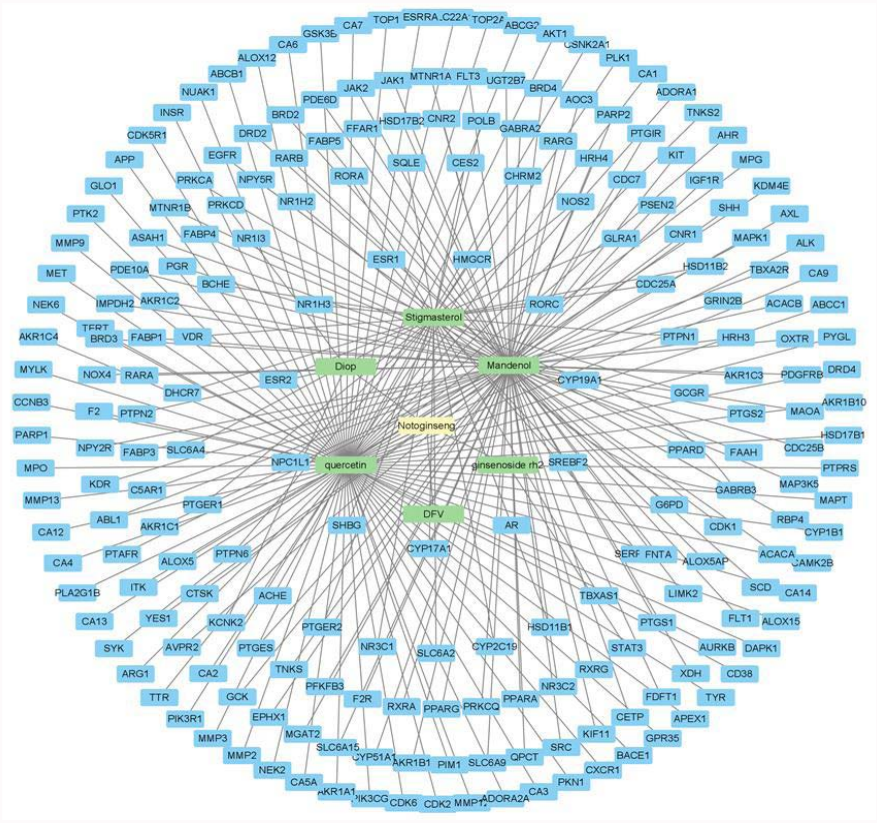

Figure 2: Active ingredient-target network.

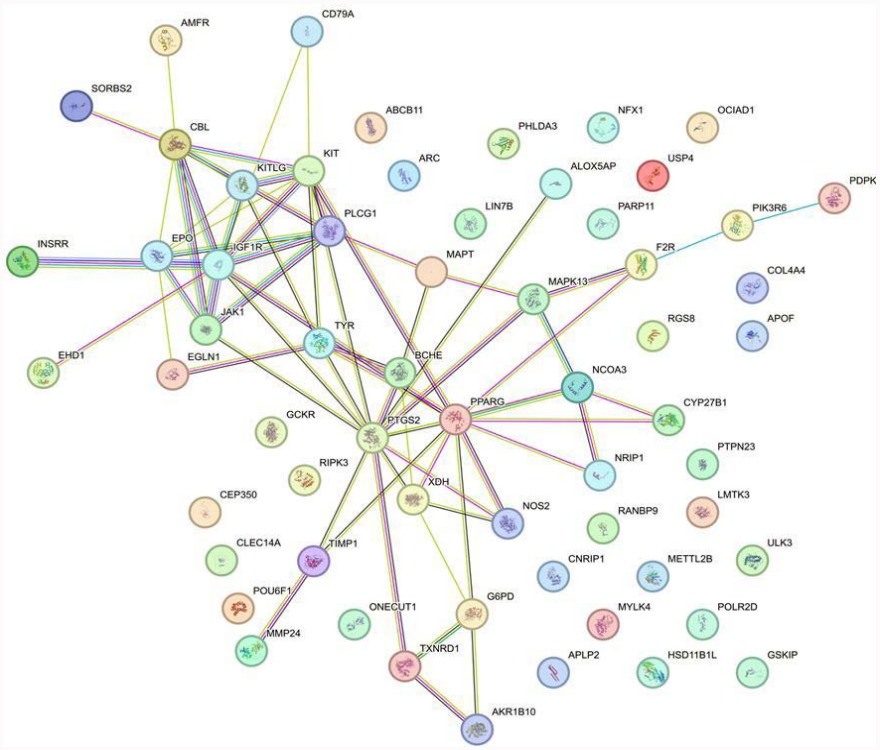

Figure 3: Topological analysis diagram of PPI network of target protein.

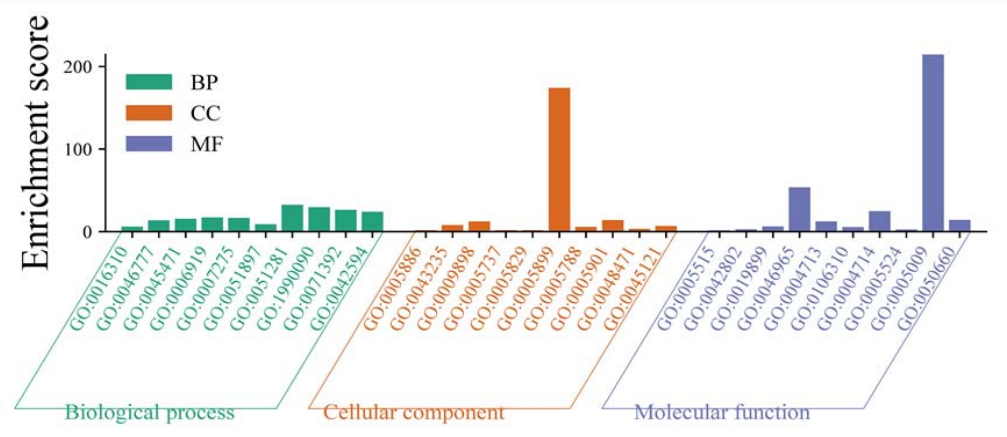

Figure 4: Go enrichment analysis of targets.

of Molecular Function (MF), which mainly involved protein tyrosine kinase activity (protein tyrosine kinase); response to inorganic substance; Molecular function (Molecular function) 20 entries, mainly involving protein tyrosine kinase activity; hormone binding; nuclear receptor activity (nuclear receptor activity), etc.; cellular component CC (cellular component) 18 entries, mainly involved in the cell membrane raft (membrane raft); receptor complex (receptor complex); vesicle lumen (vesicle lumen), etc. GO Enrichment analysis thermogram, see Figure 4.

The results of KEGG analysis were plotted as a bubble diagram, which showed that the targets of Panax ginseng for the treatment of diabetic ophthalmopathy were mainly enriched in the cancer signaling pathway in diabetic complications, EGFR signaling pathway. See Figure 5.

Discussion

In this study, a total of eight active ingredients of Panax ginseng with targets were identified using the TCMSP online database and reviewing the literature: Mandenol, DFV, Diop, beta-sitosterol, stigmasterol, ginsenoside rh2, ginsenoside f2, and quercetin. We searched and sorted out the relevant target genes of diabetic eye disease, then compared them with the target genes of Panax ginseng's effective active ingredients for intersection, and obtained 77 common genes and 6 compounds with relatively good activity. There were 292 targets for the treatment of diabetic ophthalmopathy by Panax ginseng, and GO enrichment analysis of the targets revealed that the targets for the treatment of diabetic ophthalmopathy by Panax ginseng were mainly enriched in response to hormone, pathways in cancer, response to inorganic substance, molecular function, and

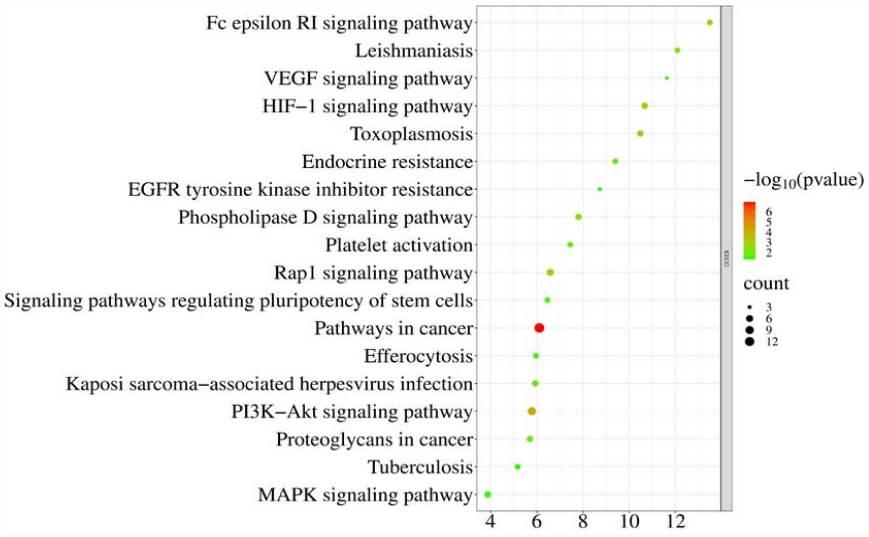

Figure 5: KEGG enrichment analysis of targets.

molecular function); Molecular Function (MF) and other targets. Biological processes are mainly involved in protein tyrosine kinase activity, hormone binding and nuclear receptor activity.

Nine core targets were obtained in this study: PPARG, PLCG1, PTGS2, KIT, NCOA3, KITLG, VDR, and CBL and IGFIR. PPARG, a member of the nuclear hormone receptor superfamily (steroids, thyroxine, vitamin D, etc.), is one of the most important molecules for adipocyte differentiation and metabolic regulation *in vivo*, and is required for adipose tissue differentiation [17], and is involved in the integration of energy metabolism, adiposeness and differentiation, and glucose homeostatic control. In recent years, extensive studies on the mechanism of diabetic ophthalmopathy have concluded that it is a multigene involved stage disease involving immune-inflammatory response, VEGF gene and miRNA gene regulation [18,19]. KEGG pathway enrichment analysis was performed to demonstrate that the target genes were significantly enriched in bacterial invasion of epithelial cells, AMPK signaling pathway, osteoblast differentiation, adhesive linkage, and PI3K-Akt signaling pathway. The STRING database was also applied to verify the PPARG gene, suggesting that PPARG is involved in the AMPK signaling pathway and adhesion junction. And the signaling pathway that intersected with KEGG results was also the AMPK signaling pathway and adhesion junction, suggesting that PPARG gene may regulate the development of T2DR (Type 2 diabetic retinopathy) through the AMPK signaling pathway and adhesion junction signaling pathway [20]. Through bioinformatics analysis, it is broadly plausible that PPARG may affect the development of diabetic ophthalmopathy through mechanisms such as the AMPK signaling pathway and adhesive linkage.

As natural medicines, traditional single, isolated, and static studies are often difficult to identify the process of their treatment, and the potential of many active ingredients can only be elucidated in the network.

The present study systematically investigated and pointed out the relationship between the active chemical components, target genes, related biological signaling pathways and diabetic eye disease, providing a theoretical basis for further research on the mechanism of action of Panax ginseng and for the development of new drugs.

Conclusion

In this experiment, we screened 8 active chemical components of Panax ginseng, 147 key targets, 1366 key targets of diabetic eye disease, and 77 overlapping targets in the intersection of the two. For the enrichment analysis of the intersected targets, it was found that the treatment of diabetic eye disease by Panax ginseng works through 16 KEGG and 58 GO-related signaling pathways. Meanwhile, in the knowledge-based network construction method, it is able to deal with massive data in a short period of time and has better reproducibility of results with constant rules and less dependence on the experimenter's own knowledge level. Relying on the current situation of explosive growth of biological information, text mining technology has become more and more solid in the field of data collection. The above similarity-based association discovery algorithm analyses structural data, histological data and other information to construct interconnections among drugs, targets and diseases, thus providing assistance for research on drug potential target prediction and new therapeutic effects of drugs.

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