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Network Pharmacology Study on the Mechanism of Qiang Huo-Yinchen Treating Diabetic Peripheral Neuropathy

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Abstract: *Objective: To explore the mechanism of Qiang huo-Yin chen in the treatment of diabetic peripheral neuropathy (DPN) based on network pharmacology. Methods Using traditional Chinese medicine system pharmacology analysis platform (TCMSP), oral bioavailability (OB) ≥30 %, drug-like (DL)≥0.18 as screening conditions, notopterygium-Yinchen compounds and related targets were obtained. DNP-related genes were obtained from the human gene database (GeneCards) and the online human Mendel genetic database (OMIM). The intersection genes between candidate compounds and DNP were obtained by online Wayne diagram analysis. The interaction network of intersection proteins was constructed by STRING 10.0 database. Gene ontology (GO) analysis and signal pathway enrichment analysis based on Kyoto Encyclopedia of Genes and Genes (KEGG) were performed on the intersection proteins through DAVID database. Cytoscape 3.8.2 software was used to construct the component-target-signaling pathway network of Radix Astragali- Radix Angelicae Sinensis in the treatment of diabetic nephropathy. Results: The constructed component-target network contained 23 active components, including cnidilin, quercetin, beta-sitosterol, isorhamnetin, and areapillin. HSP90AA1, BLC2, CASP3 among 63 targets, KEGG involves 28 pathways such as lipid and atherosclerosis, AGE-RAGE in diabetic complications, apoptosis, pathway signaling pathways of neurodegenerative diseases. Conclusion: Qianghuo-yinchen pair may act on HSP90AA1, BLC2, CASP3 and other targets through multiple components such as quercetin and β-sitosterol, and regulate multiple signaling pathways such as lipid, apoptosis, and neurodegenerative diseases, thereby playing a role in the treatment of DNP.*

Keywords: *Notopterygium, Yinchen, Diabetic peripheral neuropathy, Network pharmacology, Target, Pathway*

1. Introduction

DNP is a common chronic complication of diabetes. Hyperglycemia is the main cause of DPN, and its pathogenesis is not clear. It is generally believed to be related to multiple factors, including metabolic disorders, nerve cell damage, cellular oxidative stress, immune factors and mitochondrial dysfunction. The main predisposing factors are hyperglycemia and hyperlipidemia. Smoking and drinking may also be related to the occurrence of diabetic peripheral neuropathy.

DPN belongs to the category of Bi syndrome of diabetes in traditional Chinese medicine. Deficiency of liver and kidney, spleen loss of health transport as the basis, wind cold and damp heat, phlegm turbidity, blood stasis blocking meridians as the standard, belongs to the deficiency of origin and excess syndrome. Doctors in the past dynasties especially emphasized that qi deficiency was easy to cause retention of dampness, and yin deficiency was easy to produce heat accumulation, indicating that water dampness tended to heat up, and the occurrence of dampness and heat accumulation was a common syndrome of qi and yin deficiency [1]. Notopterygium, pungent taste, warm nature, return to the bladder meridian, kidney meridian, with pungent dispelling wind, dry Shengshi, Tongbi Zhitong; yinchen, bitter taste, mild cold, liver and gallbladder, spleen and stomach meridian, bitter diarrhea decreased, heat and dampness, but the disease clinical symmetry pain and sensory abnormalities, lower limb symptoms more common than upper limbs. 'Herbal extract' says that it can 'stagnate the meridians due to pathogenic wind-dampness and heat, and the qi and blood flow are not smooth, so it is annoyed all over the body and limbs'. The two drugs are used together to warm and retain cold, with one bitterness and one bitterness.

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In addition, the meridians and collaterals of the foot and lower limbs are all based on the Foot-Yang Meridian and Foot-Yin Meridian, namely, the Foot-Yangming Gastric Meridian, the Foot-Shaoyang Bile Meridian, the Foot-Taiyang Bladder Meridian outside the lower limb, and the Foot-Taiyin Spleen Meridian inside the lower limb, the Foot-Jueyin Liver Meridian, and the Foot-Shaoyin Kidney Meridian inside the lower limb. These six meridians are precisely Qianghuo – Fangfeng meridian. The combination of the two drugs can disperse the exterior and clear the interior, so that the pathogenic wind, dampness and heat can be separated from the interior. Tong Xiaolin believes that the main pathogenesis of DPN is based on qi deficiency, yin deficiency and yang deficiency, marked by stagnation of blood stasis and collaterals, invasion of pathogenic wind, cold and dampness, and stagnation of collaterals throughout the whole course of DPN [2]. Professor Fan Guanjie believes that the pathogenesis of DPN is a process of chronic attack, which is closely related to emotional factors. Therefore, the treatment of Baishao, Yinchen and other drugs as the core into the liver meridian, fully embodies the ' dynamic - sequential eight methods ' to grasp the core pathogenesis of DPN, from the liver on the treatment of DPN academic thought [3]. Modern pharmacological studies have shown that Notopterygium Notopterygium has anti-inflammatory, analgesic, antioxidant and other pharmacological effects. In the rat model of neuropathic pain, the aqueous extract of Notopterygium Notopterygium can inhibit the expression of P2X4R in the spinal cord and reduce the level of inflammation, thereby alleviating the neuropathic pain in rats [4]. Yinchen can regulate glucose and lipid metabolism [5]. The compatibility of the two drugs (Danggui Niantong Decoction) can not only effectively improve the motor and sensory nerve conduction velocity of median nerve and common peroneal nerve, but also improve the clinical symptoms of patients more effectively [6]. Modern medicine through experiments [7] also confirmed that Danggui Niantong Decoction has a certain anti-inflammatory analgesic, promote tissue blood circulation.

In this paper, the molecular mechanism of action was studied, and the pharmacological mechanism of Qianghuo-Yinchen in the treatment of DPN has not been reported. Therefore, this paper used the method of network pharmacology to explore the target and signaling pathway of DPN according to its chemical composition. To provide reference for better clinical application of the drug pair.

2. Methodology

1) Screening of Notopterygium Notopterygium-Yinchen Compounds The effective components of Notopterygium Notopterygium and Yinchen were searched by TCMSP and http://lsp.nwu.edu.cn/tcmspsearch.php), respectively. The oral bioavailability (OB) ≥ 30 % and drug likeness (DL) ≥ 0.18 were selected as the criteria.

2) Compounds and DPN target screening Using TCMSP analysis platform to find out the corresponding targets of compounds, and through UniProt (https://www.uniprot.org/)database query and standardize its name. Using GeneCards data platform, online human Mendelian genetics (https://www.genecards.org/; https://omim.org/)) and other two databases, with ' Diabetic peripheral neuropathy ' as the keyword, the disease targets related to DNP were searched.

3) Alignment protein screening uploads the active component-related targets and disease-related targets to online Wayne diagram (https://bioinfogp.cnb.csic.es/tools/venny/index.html)) for analysis, so as to obtain the intersection protein of compound and DNP.

4) Construction of component-target-signaling pathway network the information of intersection protein and active components and the interaction information of intersection protein signaling pathway were imported into Cytoscape 3.8.2 software to obtain the intersection protein-component interaction network, and the component-target-signaling pathway network of Qianghuo-Yinchen herb pair in the treatment of DNP was constructed.

5) Protein-protein interaction (PPI) network construction The PPI of Qianghuo-Yinchen herb pair and DNP was uploaded to STRING 10.0 (https://string-db.org/cgi/input.pl)database). Homo sapiens was selected as the research species, and PPI score was set to be > 0.4, so as to obtain the interaction relationship between the intersection proteins.

6) Gene ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genes (KEGG) signaling pathway enrichment analysis of intersection protein function and biological pathway analysis in order to further explore the biological processes and signaling pathways involved in intersection protein, the intersection protein was uploaded to DAVID database (https://david.ncifcrf.gov/),) and the data results were visualized.

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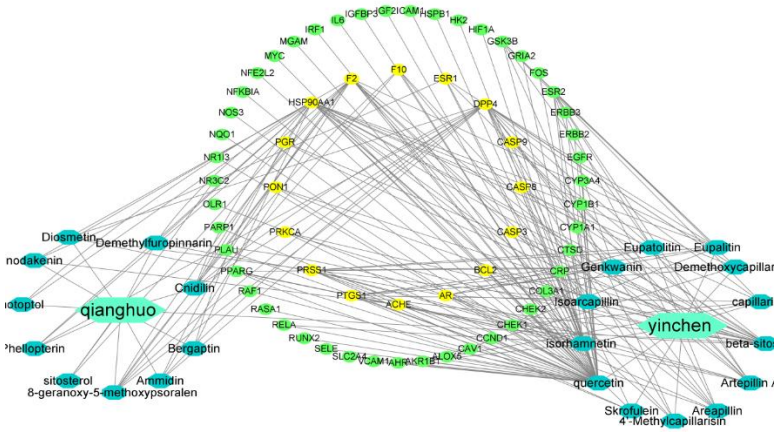
3. Results

1) Compound screening: 53 compounds in Yinchen and 185 compounds in Notopterygium Notopterygium were identified by TCMSP analysis platform, with a total of 238 compounds. With OB≥30 % and DL≥0.18 as the screening conditions, 28 compounds were finally obtained, including 13 components in Rhizome, 15 components in Notopterygium, and 1 common component in Notopterygium and Rhizome. Using TCMSP The target information of each component was found in the platform. The basic information of Qianghuo-Yinchen herb pair compounds and the compounds were shown in table 1.

Table 1: Basic information and compounds of Qianghuo-Yinchen herb pair

Molecular number	Molecular name	OB/%	drug-likeness	source
MOL001941	Ammidin	34.55	0.22	Qianghuo
MOL011962	6'-Feruloylnodakenin	32.02	0.67	Qianghuo
MOL011963	8-geranoxy-5-methoxypsoralen	40.97	0.5	Qianghuo
MOL011968	coumarin,glycoside	33.07	0.78	Qianghuo
MOL011969	Demethylfuropinnarin	41.31	0.21	Qianghuo
MOL011971	diversoside_qt	67.57	0.31	Qianghuo
MOL011975	notoptol	62.97	0.48	Qianghuo
MOL001951	Bergaptin	41.73	0.42	Qianghuo
MOL001956	Cnidilin	32.69	0.28	Qianghuo
MOL000359	sitosterol	36.91	0.75	Qianghuo
MOL004792	nodakenin	57.12	0.69	Qianghuo
MOL000358	beta-sitosterol	36.91	0.75	Qianghuo
MOL001942	isoimperatorin	45.46	0.23	Qianghuo
MOL002644	Phellopterin	40.19	0.28	Qianghuo
MOL002881	Diosmetin	31.14	0.27	Qianghuo
MOL000354	isorhamnetin	49.6	0.31	Yinchen
MOL000358	beta-sitosterol	36.91	0.75	Yinchen
MOL004609	Areapillin	48.96	0.41	Yinchen
MOL005573	Genkwanin	37.13	0.24	Yinchen
MOL007274	Skrofulein	30.35	0.3	Yinchen
MOL008039	Isoarcapillin	57.4	0.41	Yinchen
MOL008040	Eupalitin	46.11	0.33	Yinchen
MOL008041	Eupatolitin	42.55	0.37	Yinchen
MOL008043	capillarisin	57.56	0.31	Yinchen
MOL008045	4'-Methylcapillarisin	72.18	0.35	Yinchen
MOL008046	Demethoxycapillarisin	52.33	0.25	Yinchen
MOL008047	Artepillin A	68.32	0.24	Yinchen
MOL000098	quercetin	46.43	0.28	Yinchen

2) Cytoscape 3.8.2 software was used to construct the Qianghuo-Yinchen component-target network, as shown in Figure 1.



Note: green hexagon is the corresponding active ingredient, green round notopterygium-Yinchen non-intercrossing related targets, yellow dots intersection targets

Figure 1: Notopterygium qianghuo-yinchen compound-target network

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The figure includes 90 nodes and 295 edges; among them, some compounds have no corresponding targets, the left circle represents 16 effective components of Notopterygium incisum, the right circle represents 13 effective components of Artemisia capillaris, and the total target is 63. There are 16 intersection proteins of Notopterygium incisum and Artemisia capillaris, including 1 target associated with Notopterygium alone and 46 targets associated with Artemisia capillaris alone. The results of network topology analysis show that the node with high medium value of the network is the core node of the network. Such as cnidilin, quercetin, beta-sitosterol, isorhamnetin, Areapillin and other effective chemical constituents and targets HSP90AA1, BLC2, CASP3, CASP8, CASP9, PRSS1, F2, DPP4 may be the key compounds and nodes of the drug pair to play a clinical role.

3) The intersection proteins between Notopterygium incisum-Yinchen and DPN Using TCMSP analysis platform to query194proteins related to Yinchen, 15proteins related to Yinchen, 5639 proteins related to DPN were searched by CeneCard and OMIM database, and16intersection proteins were found between the corresponding targets of Notopterygium incisum-Yinchen compounds and DPN-related proteins by online Wayne diagram, respectively. PTGS1, ESR1, AR, DPP4, HSP90AA1, PRSS1, F2, ACHE, PGR, BCL2, CASP9, CASP3, CASP8, PRKCA, PON1, F10. There are17intersection proteins between DPN and Notopterygium, 62intersection proteins between DPN and Yinchen, as shown in Figure 2.

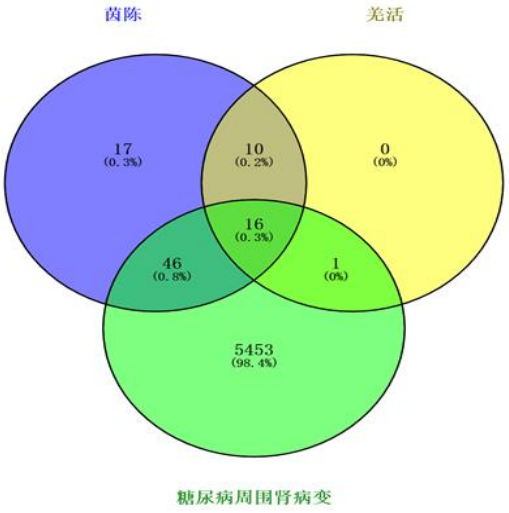

Figure 2: Venn map of qianghuo - Yinchen and DPN

4) As shown in Fig. 3, PPI network uploads 17 interacting proteins to online STRING 10.0 database, and obtains the interaction network between interacting proteins by hiding two nodes interrupted by the network. The number of nodes represented a total of 16 proteins, and the number of edges was 33; average node degree: 3.88; average local clustering coefficient: 0.70689 edges, the number of each edge represents the interaction between proteins, the more lines represent the close association between intersection proteins. BCL2, HSP90AA1, CASP3 (apoptosis-related cysteine peptidase), CASP8 (apoptosis-related cysteine peptidase), CASP9 (apoptosis-related cysteine peptidase) have strong interaction with other proteins in the network.

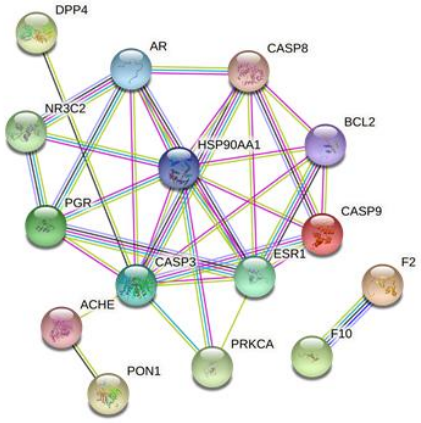

Figure 3: Interaction network between Qianghuo-Yinchen and DPN intersection protein

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5) Target pathway analysis Uploaded the intersection protein to DAVID database for GO functional enrichment analysis. 28 signaling pathways were screened by KEGG pathway enrichment, as shown in Figure 5. It involves lipid and atherosclerosis signaling pathway, AGE-RAGE signaling pathway in diabetic complications, and pathways of neurodegeneration-multiple diseases. These signaling pathways are closely related to diabetic peripheral neuropathy. The signaling pathway involving more intersection proteins may be the key signaling pathway of Qianghuo-Yinchen in the treatment of DPN. Taking two of the signaling pathways involving more intersection proteins as examples, the signaling pathways involved in the drug pair were analyzed.

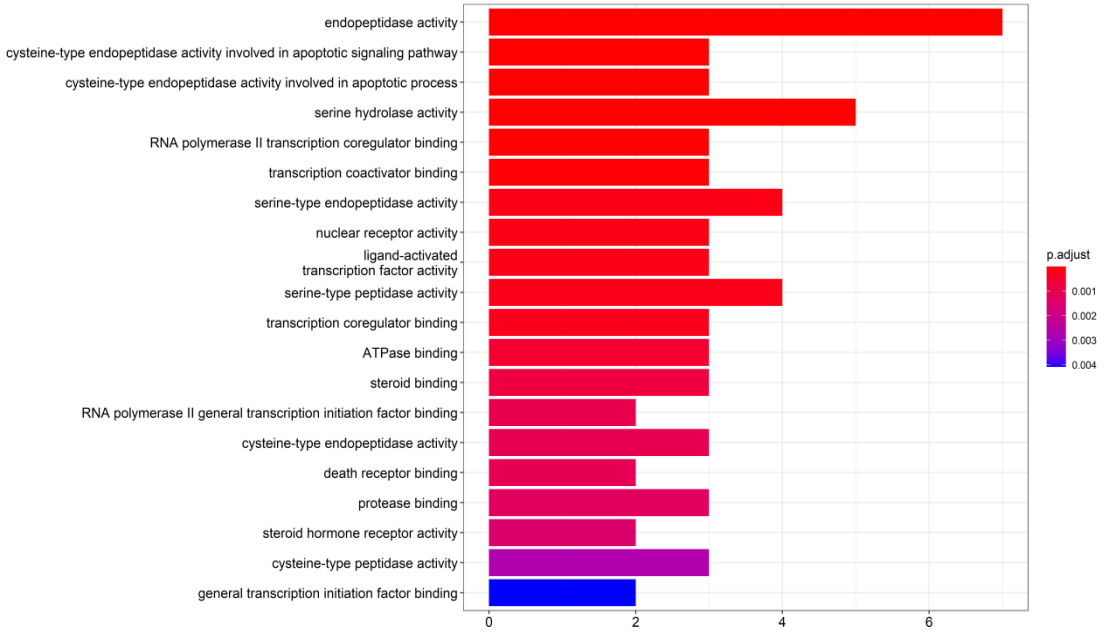

Figure 4: GO function analysis of Qianghuo-Yinchen and DPN intersection protein

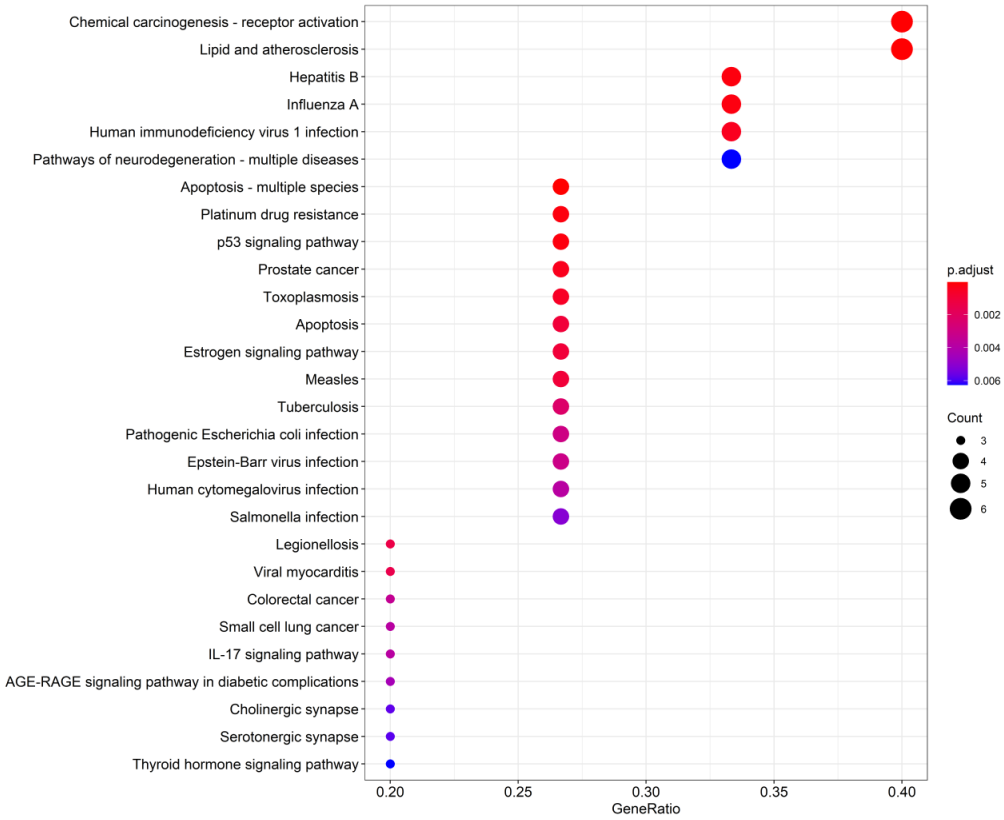

Figure 5: KEGG signaling pathway analysis of Qianghuo-Yinchen and DPN

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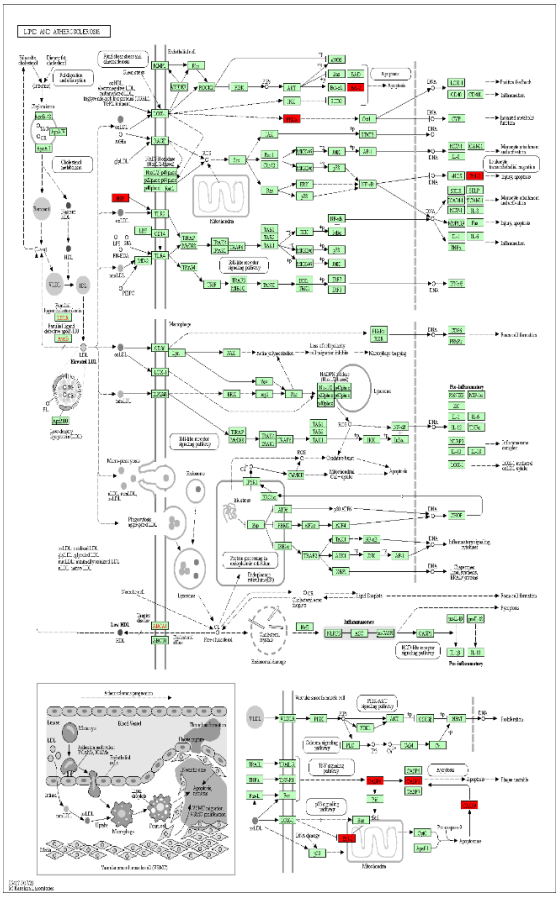


Figure 6: Lipid and atherosclerosis signaling pathway

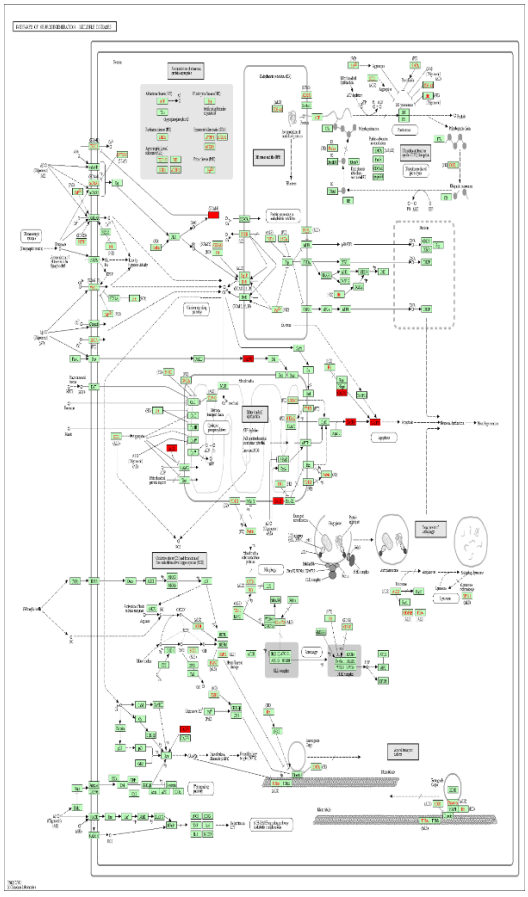
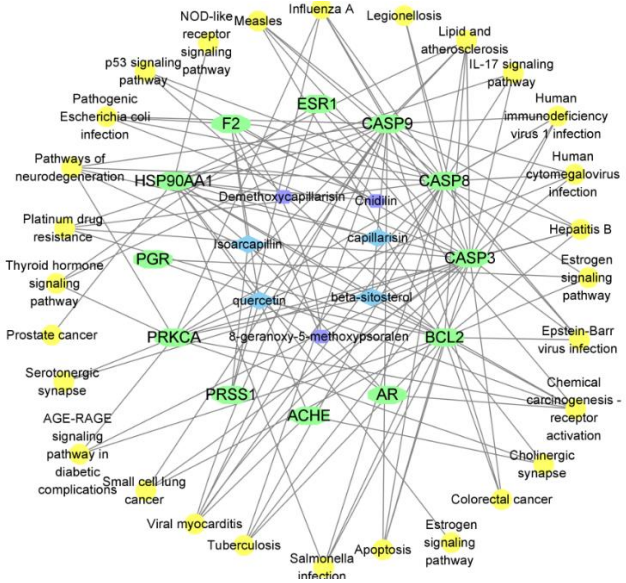


Figure 7: Pathway signaling pathway of neurodegenerative diseases

6) Component-target-signaling pathway network the component-target-signaling pathway network of Qianghuo-Yinchen treating diabetic peripheral neuropathy was constructed by Cytoscape 3.8.2 software, as shown in Figure 8.



Note: Blue rhombus represents the active ingredient of Notopterygium incisum. Purple hexagon represents the active ingredients of Yinchen. The green dots represent the drug pair related targets. Yellow yellow dots represent related pathways

Figure 8: Component-target-signal pathway network of Qianghuo-Yinchen in the treatment of diabetic peripheral neuropathy

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The map includes 7 active components and 12 potential targets, involving 28 signaling pathways. The components with high medium value in the network are quercetin, capillary protease, etc. The targets with high degree values were BCL2, CASP3, CASP8 and CASP9; it involves lipid and atherosclerosis, AGE-RAGE in diabetic complications, pathways of neurodegenerative diseases, etc. According to the signal pathway network, Qianghuo-Yinchen herb pair plays a role in the treatment of DPN from individual to whole.

4. Discussion

In recent years, studies have found that Qianghuo and Yinchen have obvious pharmacological activities in the treatment of DPN, such as regulating blood lipids, neuroprotective, anti-inflammatory, analgesic, antioxidant and so on. Lowering blood lipids and regulating the expression of related cytokines can reduce neurological impairment and improve neurological function. In this study, the main material basis and pharmacological mechanism of Qianghuo-Yinchen in the treatment of DPN were discussed from the overall perspective by using the network pharmacology method and through its drug pair components, targets and signaling pathways. The component-target-signal pathway network of Qianghuo-Yinchen in the treatment of DPN involves 8-geranoxy-5-methoxypsoralen, Phellopterin, cnidilin, demethylfuropinnarin, quercetin, Isoarcapillin, β-sitosterol, isorhamnetin and Areapillin. Modern pharmacological studies have shown that mitochondrial damage plays an important role in the occurrence and progression of DPN. Quercetin corrects mitochondrial abnormalities by activating AMPK/PGC-1α pathway in vivo and in vitro, thereby reducing diabetic peripheral neuropathy. Oxidative stress and inflammatory response play an important role in the development of DPN. β-sitosterol can regulate blood glucose by increasing the activities of insulin receptor and glucose transporter 4 in adipose tissue [8-9], Isorhamnetin can be located downstream of insulin signaling pathway by regulating AKT / FOXO1 (AKT / FOXO1 signaling pathway), which is an important way to regulate glycogen synthesis and maintain glucose homeostasis. Signaling pathway improves insulin resistance of HepG2 cells induced by high concentration of insulin [10]. In vitro studies showed that Qianghuo decoction and alcohol precipitation could inhibit the platelet aggregation time, thrombosis growth rate, platelet thrombosis, and fibrin thrombosis in isolated rabbit blood, reduce the length and dry weight of thrombosis, and prolong the formation time of thrombosis in vitro [11]. The above components predicted by network pharmacology can improve the occurrence and development of DPN through various ways, and play an important role in the treatment of diabetic peripheral neuropathy. The components of M956 (cnidilin), M354 (isorhamnetin) and M039 (Isoarcapillin) in the network have not been reported related to the treatment of DPN, which can be used as the object of future research. The targets with high medium value of component-target-signal pathway network include BCL2, CASP3, PRCKA, etc. Studies have shown that with the prolongation of diabetic rats, the apoptosis rate of dorsal root ganglion neurons in diabetic rats gradually increases, and BCL2, as the main cell regulatory gene, decreases [12]. Caspase-3 protein expression and apoptosis of dorsal root ganglion neurons in diabetic rats were significantly correlated with DNA oxidative damage, which supported oxidative damage leading to apoptosis [13,14]. Some experiments have shown that compared with the blank group, the experimental group can reduce the phosphorylation of p38 protein by down-regulating the expression of PRKCA mRNA and protein, and inhibit the proliferation and migration of vascular smooth muscle cells, thereby reducing vascular endothelial injury, anti-inflammatory and lipid-lowering effects [15]. These results suggest that these targets may be the key targets of Qianghuo-Yinchen in the treatment of DPN. In this study, the component-target-signaling pathway network of Qianghuo-Yinchen in the treatment of DPN mainly involves lipid and atherosclerosis, AGE-RAGE in diabetic complications, pathway of neurodegenerative diseases, Nod-like receptor signaling pathway and other signaling pathways. DPN is mainly caused by microvascular lesions caused by metabolic abnormalities caused by hyperglycemia. Studies have shown that [16] the up-regulation of lipid in DPN rats improves the pathological changes of autophagy disorder and sciatic nerve, and the overexpression of lipin1 in RSC96 cells also significantly reduces the excessive autophagy activity and apoptosis caused by hyperglycemia. Therefore, it is speculated that Qianghuo-Yinchen pair may affect the metabolism and apoptosis of the body by regulating the lipid and atherosclerosis signaling pathways, and the signaling pathways of neurodegenerative diseases, so as to play a role in the treatment of DPN.

In summary, this study found that the frequencies of CASP3, CASP8, CASP9 and BCL2 were repeated, so it was speculated that Qianghuo-Yinchen might regulate and inhibit neuronal apoptosis by regulating CASP3, CASP8, CASP9 and BCL2 and other targets, so as to treat DPN. At the same time, it might play a role in delaying the course of DPN by regulating the apoptosis pathway, as well as signaling pathways such as lipid and atherosclerosis, AGE-RAGE in diabetic complications and neurodegenerative

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diseases. However, due to the limitations of network pharmacology, the above conclusions need to be verified by pharmacological and clinical experiments.

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