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Network pharmacology of Angelica and Salvia in combination to modulate iron death against diabetic peripheral neuropathy

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Abstract: *Using network pharmacology to investigate the molecular mechanism of action of Angelica sinensis and Salvia miltiorrhiza in modulating iron death against diabetic peripheral neuropathy. The TCMSP database was used to obtain the active ingredients of Angelica sinensis and Salvia miltiorrhiza; the SwissTargetPrediction database was used to obtain the targets of each active ingredient. The GeneCards, DrugBank, and OMIM databases were used to obtain the targets of diabetic peripheral neuropathy. Venn online tool was used to obtain the common targets of Angelica and Dan involved in diabetic peripheral neuropathy. Gene Ontology (GO) enrichment analysis, and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were performed using R language. The FerrDb database was used to obtain iron death-related gene targets, and the relationship between Angelica, Salvia, diabetic peripheral neuropathy, and iron death was obtained. Sixty-seven active ingredients of Angelica sinensis and Salvia miltiorrhiza were obtained, and 10 gene targets of Angelica sinensis and Salvia miltiorrhiza were predicted to regulate iron death against diabetic peripheral neuropathy. The anti-diabetic peripheral neuropathy effect was achieved by regulating the iron death process through signaling pathways such as the HIF-1 signaling pathway, micro RNA, and IL-17 signaling, to investigate the multi-component, multi-target, and multi-pathway features of Angelica sinensis and Salvia miltiorrhiza in regulating iron death against diabetic peripheral neuropathy using network pharmacology, and to investigate the possible gene targets and signaling pathways of Angelica sinensis and Salvia miltiorrhiza in regulating iron death against diabetic peripheral neuropathy.*

Keywords: *angelica; salvia; diabetic peripheral neuropathy; network pharmacology; iron death*

1. Introduction

Diabetic peripheral neuropathy (DPN) is the most common chronic complication of diabetes, affecting about 50% of people with long-term diabetes, and between 16% and 24% of those with DPN face neuropathic pain [1]. The clinical presentation is characterized by bilateral, symmetrical numbness, pain or sensory abnormalities in the distal extremities, and the pathogenesis of DPN is not yet fully understood. [2]. Iron death is a regulated cell death caused by iron-dependent lipid peroxidation. [3]. Studies have shown that high dietary iron promotes the development of DPN, and since iron induces oxidative stress, which is a cause of DPN, control of dietary iron intake is important for the prevention and treatment of DPN in patients with type 2 diabetes [4]. The relationship between iron death and DPN is not yet clear, and clinical treatments and drugs for DPN are not yet a complete cure for the disease [5]. Therefore, there is an urgent need to further explore the pathogenesis of DPN and provide effective prevention and treatment methods.

Diabetic peripheral neuropathy belongs to the category of "paralysis" in Chinese medicine, which is caused by the internal stasis of blood due to the pathogenesis of Yin deficiency and dry heat in diabetes, resulting in Qi deficiency and blood stasis. [6] This is a result of the internal stasis of blood and qi deficiency. As traditional Chinese medicine, Salvia miltiorrhiza and Radix Angelicae Sinensis both have the effect of activating blood stasis and are often used in combination. Chen Haihong, Chen Bing, Chen Simiao[7] The combination of Salvia miltiorrhiza and Radix Angelicae Sinensis was found to promote the dissolution of water-soluble tannic acid B and lipid-soluble component Tanshinone IIA, which were found to have stronger pharmacological activity. Tanshinone IIA induced the activation of Nrf2 to regulate the antioxidant gene to protect the sciatic nerve, and also inhibited the regulation of NF-κB to reduce the pain of diabetic peripheral neuropathy. [8] It also inhibits NF-κB regulation to reduce pain in

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diabetic peripheral neuropathy. Tanshinphenolic acid A can reduce the reactive oxygen species (ROS) in the sciatic nerve cells under high glucose stimulation, reduce the apoptosis of sciatic nerve cells induced by high glucose, increase the conduction velocity of sciatic nerve in mice with diabetic peripheral neuropathy, and repair the damage of myelin sheath in the sciatic nerve. [9]. Coumadin's, a methanol extract of Angelica sinensis, can effectively improve the anti-apoptotic and antioxidant effects of the pro-apoptotic factor Bax, and also reduce the inflammatory response through MAPK and other pathways for neuroprotective effects.[10] It also has a neuroprotective effect by reducing inflammation through MAPK and other pathways. It has been reported that Angelica polysaccharide, a water-soluble component of Angelica, can reduce iron load in mice with high iron load.[11] In addition, cryptotanshinone, the active component of Salvia miltiorrhiza, induced iron death in human hepatoma HepG2 cells by inhibiting the expression of glutathione peroxidase 4 (GPX4) and cysteine glutamate retrotransporter light chain protein (xCT).[12] . Although the use of Angelica sinensis and Salvia miltiorrhiza in combination is reflected in numerous prescriptions, and the medicinal effects of Chinese medicine have been continuously explored and explored, the mechanism by which Angelica sinensis and Salvia miltiorrhiza regulate iron death against diabetic peripheral neuropathy has not yet been clarified.

Network pharmacology is a new approach combining network analysis and pharmacology to explore the relationship between Chinese herbal medicine pairings, targets, diseases and pathways at the molecular level, and to elucidate the possible mechanism of the combination of Angelica and Danshen in regulating iron death in the treatment of diabetic peripheral neuropathy, providing basic data and theoretical basis for clinical treatment and application.

2. Methodology

2.1. Acquisition of chemosynthetic components and screening of gene targets in Chinese medicine

Using "Angelica" and "Salvia" as search terms, in TCMSP (https: // tcmsp. php) The active ingredients were searched in the TCMSP (https // tcmsp. php) database, and the screening criteria were set as oral bioavailability (OB) ≥ 30% and drug-like (DL) ≥ 0.18. The obtained active ingredients were Pubchem(https://pubchem.ncbi.nlm.nih.gov) The SMILES were obtained, using the SwissTargetPrediction database (https: //http://www.swisstargetprediction.ch/) The targets of each active ingredient were obtained.

2.2. Access to genetic targets for diabetic peripheral neuropathy

The search term "Diabetic Peripheral Neuropathy" was used in GeneCards (https://www.genecards.org/) , DrugBank(https://www.drugbank.com/) and OMIM (https://omim.org/) databases to identify relevant disease gene targets.

2.3. Construction of the "drug-active ingredient-target" network diagram

The drug-component-target interaction network was constructed using Cytoscape software (version 3.9.1) by integrating data from the active ingredient, target and disease intersection targets. Network Analyzer was used to calculate network topology parameters and obtain correlation values.

2.4. Construction of a gene target protein interaction network (PPI) and screening of core targets

The intersecting targets of the drugs and diseases obtained were imported into the STRING database and searched by restricting the species to "Homo Sapiens" to construct a PPI network. The CytoNCA function in Cytoscape software was used to perform a metric analysis to obtain the core gene targets.

2.5. KEGG pathway enrichment analysis and GO enrichment analysis

The R language was used to convert drug and disease target data into gene IDs, and then KEGG pathway enrichment analysis and GO enrichment analysis were performed to create bubble and histograms.

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2.6. Iron death regulatory gene acquisition for Angelica-Danshen-diabetic peripheral neuropathy triple target synthesis

The driver genes, suppressor genes and marker genes regulating iron death process were obtained from FerrDb database for integration. The Venn online tool was used to analyse the iron death regulatory genes and the common genes of Angelica and Salvia involved in diabetic peripheral neuropathy, which are the gene targets of Angelica and Salvia in the regulation of iron death in diabetic peripheral neuropathy. The KEGG pathway enrichment analysis of the common gene was performed using R language software, and the target protein interaction network was performed using the STRING database.

3. Results

3.1. Acquisition of chemosynthetic components and screening of gene targets in Chinese medicine

The TCMSP database was searched for a total of 67 compounds of "Angelica" and "Salvia", including active ingredients such as Stigmasterol, beta-sitosterol and luteolin, as shown in Table 1. End. The SwissTargetPrediction database was used to obtain a total of 922 gene targets for the active ingredients.

Table 1: Basic information on the main compound components of Angelica and Salvia

Source	MOL ID	Ingredients	OB (%)	DL
Salvia miltiorrhiza	MOL006824	α-amyrin	39.51	0.76
Salvia miltiorrhiza	MOL001659	Poriferasterol	43.83	0.76
Salvia miltiorrhiza	MOL002776	Baicalin	40.12	0.75
Salvia miltiorrhiza	MOL001771	poriferast-5-en-3beta-ol	36.91	0.75
Salvia miltiorrhiza	MOL007142	salvianolic acid j	43.38	0.72
Salvia miltiorrhiza	MOL007051	6-o-syringyl-8-o-acetyl shanzhiside methyl ester	46.69	0.71
Salvia miltiorrhiza	MOL007063	przewalskin a	37.11	0.65
Salvia miltiorrhiza	MOL007141	salvianolic acid g	45.56	0.61
Salvia miltiorrhiza	MOL007081	Danshenol B	57.95	0.56
Salvia miltiorrhiza	MOL007093	dan-shexinkum d	38.88	0.55
Salvia miltiorrhiza	MOL007082	Danshenol A	56.97	0.52
Salvia miltiorrhiza	MOL007071	przewaquinone f	40.31	0.46
Salvia miltiorrhiza	MOL007150	(6S)-6-hydroxy-1-methyl-6-methylol-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-quinone	75.39	0.46
Salvia miltiorrhiza	MOL007151	Tanshindiol B	42.67	0.45
Salvia miltiorrhiza	MOL007152	Przewaquinone E	42.85	0.45
Salvia miltiorrhiza	MOL007070	(6S,7R)-6,7-dihydroxy-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione	41.31	0.45
Salvia miltiorrhiza	MOL007079	tanshinaldehyde	52.47	0.45
Salvia miltiorrhiza	MOL007155	(6S)-6-(hydroxymethyl)-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione	65.26	0.45
Salvia miltiorrhiza	MOL007045	3α-hydroxytanshinone IIa	44.93	0.44
Salvia miltiorrhiza	MOL007064	przewalskin b	110.32	0.44

Continued Table Basic information on the main compound components of Angelica-Dangshen

Source	MOL ID	Ingredients	OB (%)	DL
Salvia miltiorrhiza	MOL007120	miltionone II	71.03	0.44
Salvia miltiorrhiza	MOL007058	formyltanshinone	73.44	0.42
Salvia miltiorrhiza	MOL007068	Przewaquinone B	62.24	0.41
Salvia miltiorrhiza	MOL007059	3-beta-Hydroxymethyllenetanshiquinone	32.16	0.41
Salvia miltiorrhiza	MOL007069	przewaquinone c	55.74	0.4
Salvia miltiorrhiza	MOL002651	Dehydrotanshinone II A	43.76	0.4
Salvia miltiorrhiza	MOL007154	tanshinone iia	49.89	0.4
Salvia miltiorrhiza	MOL007111	Isotanshinone II	49.92	0.4
Salvia miltiorrhiza	MOL007050	2-(4-hydroxy-3-methoxyphenyl)-5-(3-hydroxypropyl)-7-methoxy-3-benzofurancarboxaldehyde	62.78	0.4
Salvia miltiorrhiza	MOL007088	cryptotanshinone	52.34	0.4
Salvia miltiorrhiza	MOL007108	isocryptotanshi-none	54.98	0.39
Salvia miltiorrhiza	MOL007085	Salvilenone	30.38	0.38
Salvia miltiorrhiza	MOL007121	miltipolone	36.56	0.37
Salvia miltiorrhiza	MOL007127	1-Methyl-8,9-dihydro-7H-naphtho[5,6-g]benzofuran-6,10,11-trione	34.72	0.37
Salvia miltiorrhiza	MOL007061	Methylenetanshinquinone	37.07	0.36
Salvia miltiorrhiza	MOL007101	dihydrotanshinone I	45.04	0.36
Salvia miltiorrhiza	MOL001601	1,2,5,6-tetrahydrotanshinone	38.75	0.36
Salvia miltiorrhiza	MOL007132	(2R)-3-(3,4-dihydroxyphenyl)-2-[(Z)-3-(3,4-dihydroxyphenyl)acryloyl]oxy-propionic acid	109.38	0.35

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Salvia miltiorrhiza	MOL007125	neocryptotanshinone	52.49	0.32
Salvia miltiorrhiza	MOL007100	dihydrotanshinlactone	38.68	0.32
Salvia miltiorrhiza	MOL007130	prolithospermic acid	64.37	0.31
Salvia miltiorrhiza	MOL007094	danshenspiroketallactone	50.43	0.31

Continued Table Basic information on the main compound components of Angelica-Dangshen

Source	MOL ID	Ingredients	OB (%)	DL
Salvia miltiorrhiza	MOL007048	(E)-3-[2-(3,4-dihydroxyphenyl)-7-hydroxy-benzofuran-4-yl]acrylic acid	48.24	0.31
Salvia miltiorrhiza	MOL007105	epidanshenspiroketallactone	68.27	0.31
Salvia miltiorrhiza	MOL007156	tanshinone VI	45.64	0.3
Salvia miltiorrhiza	MOL007036	5,6-Dihydroxy-7-isopropyl-1,1-dimethyl-2,3-dihydrophenanthren-4-one	33.77	0.29
Salvia miltiorrhiza	MOL007098	deoxyneocryptotanshinone	49.4	0.29
Salvia miltiorrhiza	MOL007118	microstegiol	39.61	0.28
Salvia miltiorrhiza	MOL002222	sugiol	36.11	0.28
Salvia miltiorrhiza	MOL007149	NSC 122421	34.49	0.28
Salvia miltiorrhiza	MOL007140	(Z)-3-[2-[(E)-2-(3,4-dihydroxyphenyl)vinyl]-3,4-dihydroxy-phenyl]acrylic acid	88.54	0.26
Salvia miltiorrhiza	MOL000569	digallate	61.85	0.26
Salvia miltiorrhiza	MOL007122	Miltirone	38.76	0.25
Salvia miltiorrhiza	MOL007107	C09092	36.07	0.25
Salvia miltiorrhiza	MOL000006	luteolin	36.16	0.25
Salvia miltiorrhiza	MOL007145	salviolone	31.72	0.24
Salvia miltiorrhiza	MOL007123	miltirone II	44.95	0.24
Salvia miltiorrhiza	MOL007124	neocryptotanshinone ii	39.46	0.23
Salvia miltiorrhiza	MOL007041	2-isopropyl-8-methylphenanthrene-3,4-dione	40.86	0.23
Salvia miltiorrhiza	MOL007143	salvilenone I	32.43	0.23
Salvia miltiorrhiza	MOL007049	4-Methylenemiltirone	34.35	0.23
Salvia miltiorrhiza	MOL001942	isoimperatorin	45.46	0.23
Angelica	MOL000449	Stigmasterol	43.83	0.76
Angelica	MOL000358	beta-sitosterol	36.91	0.75

3.2. Key targets of Angelica-Danshen in the treatment of diabetic peripheral neuropathy

The disease targets related to diabetic peripheral neuropathy were obtained from the GeneCards, OMIM and DrugBank databases, and a total of 1616 "disease targets" were obtained using the Venn online tool, see Figure 1a. 59 disease targets and drug component targets were obtained, see Figure 1. The common targets are shown in Figure 2.

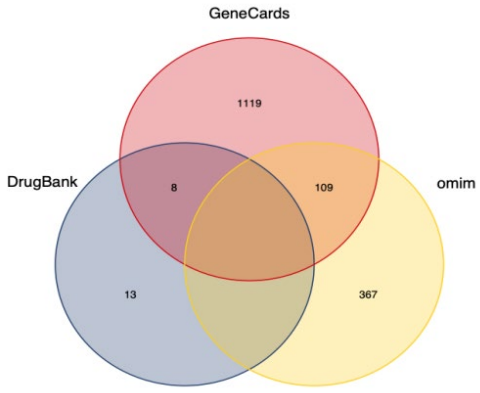

Figure 1: Disease target map

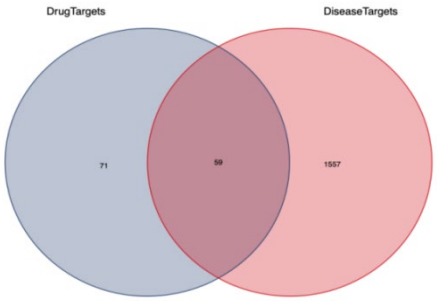

Figure 2: Intersection target map

3.3. Drug-component-target interaction network in the treatment of diabetic peripheral neuropathy with angelica-danshen

The "drug-component-target" interaction network of Angelica and Danshen for the treatment of DPN is shown in Figure 3, including 126 nodes and 473 edges. The blue circles represent the drug component Salvia divinorum; the red triangles represent the drug component Angelica; and the green squares represent the drug component's gene targets. The activity of the drug components is expressed in degrees. The top five chemical components are luteolin, dihydrotanshinlactone, 4-methylenemiltirone, tanshinone iia, and neocryptotanshinone ii.

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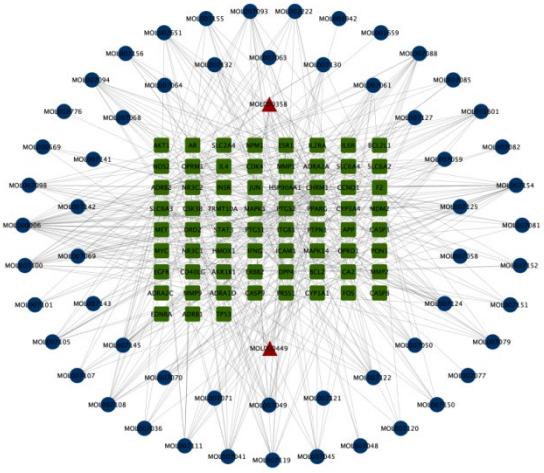

Figure 3: Drug-component-target network diagram

3.4. PPI network analysis of Angelica-Danshen for diabetic peripheral neuropathy

Using the STRING database, the PPI network graph of the targets was analysed at a confidence level of 0.400, with 59 nodes and 636 edges, see Figure 4. The core PPI network was obtained through the CytoNCA plug-in in Cytoscape software and filtered by the mean of the node degree values (degree) of the targets to obtain TP53, ICAM1, EGFR, STAT3, HSP90AA1, IFNG and MYC3, see Figure 5. These targets play a linking role in the PPI network and have a close relationship with the action of the active ingredients of Angelica and Salvia, and may become the core targets for the treatment of DPN.

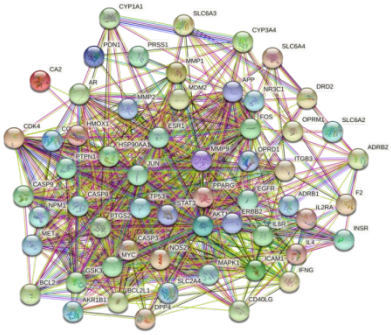

Figure 4: PPI network diagram

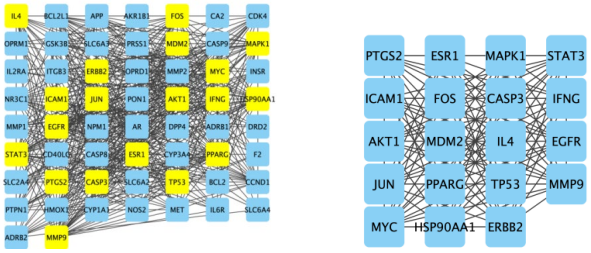

Figure 5: Core target map

3.5.GO enrichment analysis and KEGG pathway aalysis

GO and KEGG analysis of potential gene targets for DPN treatment with Angelica and Salvia. Screening was performed by the R language package. the results of GO enrichment analysis are shown in Figure 6. biological processes (BP) involved response to metal ions, response to radiation, response to oxygen levels, response to foreign stimuli and response to nutrient levels. Molecular function (MF) involves iso-DNA-binding transcription factor binding, phosphatase binding, RNA polymerase II-specific DNA-binding transcription factor binding and peptide chain endonuclease activity. Molecular targeting (CC) Gene targets are closely associated with membrane rafts, membrane micro-regions, adhesion patches, cell leading edges and cellular matrix junctions. enrichment results for the KEGG pathway are, see Figure 7, PI3K-AKT signalling pathway, human cytomegalovirus infection, lipid and atherosclerosis and endocrine resistance related pathways

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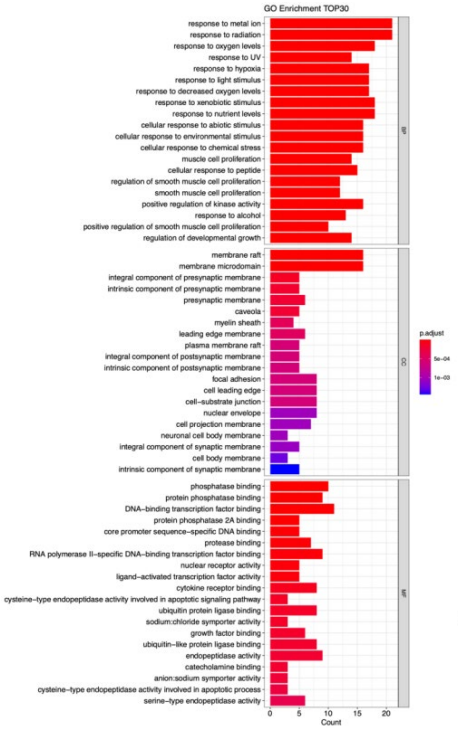

Figure 6: GO enrichment analysis

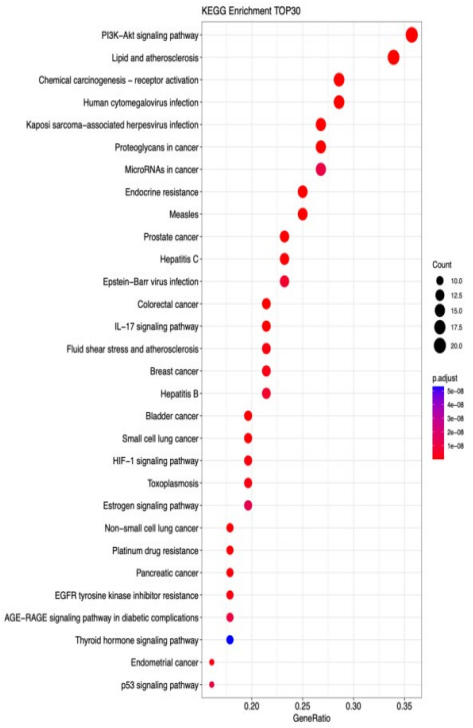

Figure 7:KEGG pathway enrichment analysis

3.6. Iron death regulatory gene acquisition for Angelica-Danshen-diabetic peripheral neuropathy triple target synthesis

The FerrDb database was used to obtain 108 driver genes, 109 suppressor genes and 123 marker genes that regulate the iron death process, and after aggregation, the non-Human and duplicate gene targets were removed and integrated to obtain a total of 214 genes. The intersection of 214 iron death-regulated genes and 59 common genes was obtained using the Venn online tool, which is shown in Figure 8. The 10 gene targets were enriched for the KEGG pathway using the R language package and the screening condition was P<0.05. The top 10 signalling pathways are shown in Figure 9. The PPI network diagram of the targets was obtained by importing the 10 gene targets into the STRING database and analysed at a confidence level of 0.400, as shown in Figure 10. In combination with the previous analysis, it can be inferred that the active ingredients of Angelica sinensis and Salvia miltiorrhiza active ingredients of Angelica sinensis regulate the HIF-1 signalling pathway, micro RNA in cancer, leishmaniasis, PD-L1 expression and PD-1 checkpoint pathway in cancer, hepatitis C, through TP53, HMOX1, NOS2, STAT3, MAPK1, PTGS2, EGFR, DPP4, IFNG, JUN gene targets and Kaposi's sarcoma-associated herpesvirus infection, among other signalling pathways regulating iron death.

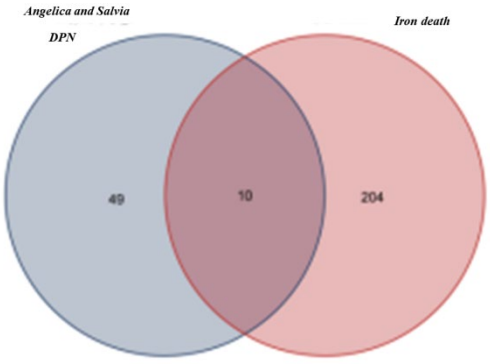

Figure 8: Intersecting targets

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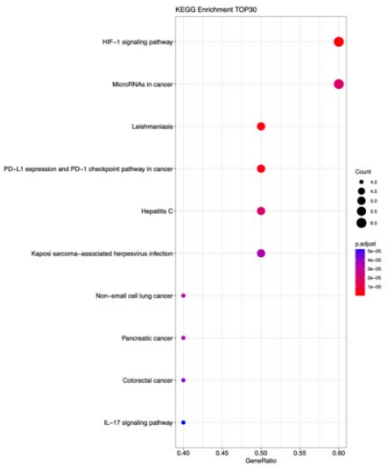

Figure 9:Diagram of the signalling pathway regulating iron death

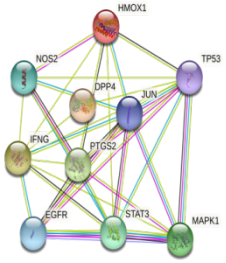

Figure 10:PPI network diagram

4. Discussion

Studies have shown that diabetic peripheral neuropathy is mainly due to hyperglycemia and insulin resistance, hypersecretion producing dyslipidemia, oxidative and nitrosative stress in the endoplasmic reticulum and mitochondria, and that this process leads to the accumulation of ROS, inflammation and cellular damage[13] . The pathogenesis of diabetic peripheral neuropathy is complex and can only be prevented and treated by improving lifestyle, lowering glucose and repairing nerves. An experimental study found that both the iron-deficient and high-iron diet groups in diabetes resulted in an increased inflammatory response in the sciatic nerve of db/db mice, and that anti-inflammatory cells in the sciatic nerve of the high-iron diet group were significantly higher than those of the low-iron diet group, suggesting that disturbances in iron homeostasis enhance the inflammatory process in the peripheral nerve[14] . In this paper, 67 active compounds of Angelica and Salvia were obtained through screening, and 59 potential targets were predicted for the treatment of diabetic peripheral neuropathy. The network diagram suggested that luteolin, dihydrotanshinlactone, 4-methylenemiltirone, tanshinone iia, neocryptotanshinone ii were the effective compounds of angelica and danshen for the treatment of diabetic peripheral neuropathy, and obtained a list of compounds based on TP53, ICAM1, EGFR, STAM1, and STAM2. ICAM1, EGFR, STAT3, HSP90AA1, IFNG, MYC and others as core gene targets. The PI3K-AKT signalling pathway, lipid and atherosclerosis and endocrine resistance signalling complexes associated with DPN were obtained by KEGG enrichment analysis. Ten common targets were obtained for iron death-regulated gene targets with Angelica, Salvia and DPN gene targets, namely: TP53, HMOX1, NOS2, STAT3, MAPK1, PTGS2, EGFR, etc. It is hypothesized that Angelica and Salvia may mediate the HIF-1 signaling pathway, micro RNA in cancer, through these 10 targets. hepatitis C and Kaposi's sarcoma-associated herpesvirus infection, among other signaling pathways that regulate iron death, in the treatment of DPN.

Tanshinone IIA is the main lipid-soluble component of Salvia miltiorrhiza, which has anti-inflammatory, antioxidant activity and neuroprotective effects.[15] It has anti-inflammatory, antioxidant and neuroprotective effects. Xu Lu, Tang Qiqiang[16] et al. found that the use of iron death inducers led to nerve cell damage, resulting in a significant increase in intracellular reactive oxygen species, lipid reactive oxygen species and reactive iron content, and that the expression of heme oxygenase 1 in cells was increased after the addition of tanshinone IIA. .

Iron death is primarily a form of iron-dependent regulation of cell death by lipid peroxidation[17] . Recent studies have identified multiple gene targets that can regulate iron death. The P53 transcriptional target CDKN1A can inhibit iron death in rectal cancer cells induced by metabolic stress due to cystine deprivation.[18] . HMOX1 (encoding heme oxygenase 1) knocked down excess Fe^{2+} , reduced iron levels and ROS, alleviated lipid peroxidation and improved the development of diabetic atherosclerosis.[19] . It was found that iron binding to CDK1 enhanced 4E-BP1 phosphorylation, thereby upregulating GP130 and activating downstream STAT3 signaling, leading to further development of lung cancer.[20] NOS2 (encoding nitric oxide synthase 2) inhibits lipid peroxidation activity against iron death, and inhibition of NOS2/iNOS increases the sensitivity of M1 macrophages to iron death, leading to a pro-inflammatory tumour environment.[21] PTGS2, known as cyclooxygenase-2, is essential for prostaglandin synthesis and can catalyze lipid oxidation leading to iron cytosis, and inhibition of PTGS2 effectively attenuates iron

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death.[22] . The lysosomal degradation process of activated EGFR contributes to the inhibition of sustained and excessive activation of EGFR signaling, which inhibits downstream NRF2 activity, with a subsequent increase in antioxidant capacity adaptation and increased ironosis in advanced hepatocellular carcinoma (HCC) cells[23] . The tumour suppressor protein p53 (TP53) can de-inhibit iron death by inhibiting the activity of DPP4 (dipeptidyl peptidase 4)[24] . These core gene targets can be involved in the iron death process through direct or indirect action, and may be the direction of research on the gene targets of Angelica and Salvia in the regulation of iron death in the treatment of diabetic peripheral neuropathy.

As a traditional blood-activating herb, the active ingredients of Salvia divinorum are effective in treating various neurological damages and have strong anti-inflammatory, anti-oxidative stress and oxygen free radical scavenging abilities.[25] It has strong anti-inflammatory, anti-oxidant stress and oxygen free radical scavenging abilities. As a traditional Chinese medicine, Angelica sinensis has high medicinal value and is widely used in clinical practice. Its active ingredient, Angelica polysaccharide, has the effects of improving anaemia and anti-inflammation, while benzophthalides have analgesic and neuroprotective effects and ferulic acid has antioxidant, hypolipidemic and antithrombotic effects.[26] The antioxidant, hypolipidemic and antithrombotic effects of ferulic acid. Angelica and Salvia are widely used for their anti-inflammatory, antioxidant and neuroprotective effects. Iron death has the same pathogenic mechanism as oxidative stress[27] . Recent studies have shown that the active ingredients of Salvia miltiorrhiza can reduce intracellular oxidative stress and inhibit the amount of reactive iron to achieve improvement in nerve cell damage. Currently, the mechanism by which Angelica and Salvia regulate the iron death process to play a role in the treatment of DPN has not been explored. In this study, network pharmacology was used to obtain the signalling pathways that may be associated with iron death. The HIF-1 signalling pathway protects neurons from apoptosis or prevents ischaemia by regulating VEDF, EPO, inducible nitric oxide synthase, haem oxygenase, and genes involved in glucose metabolism, apoptosis and resistance to oxidative stress. Hypoxia[28] IL-17 signalling stimulates inflammatory transcription factors, induces gene expression through NF-κB and activates MAPK signalling, and IL-17 signalling can also be regulated by the TRAF6 gene to limit IL-17-induced inflammation.[29] . It was shown that the phenolic acids in Salvia miltiorrhiza acted on inflammatory cell models induced by lipopolysaccharide (LPS), and the expression of cellular inflammatory factors was measured by ELISA, which showed a decrease in different inflammatory factors in different inflammatory cell models, and an increase in drug concentration and anti-inflammatory activity[30] . Tanshinone IIA was used in a rat model of diabetic peripheral neuropathy and was found to reduce blood glucose levels and improve the apoptosis of rat sciatic nerve cells, with antioxidant and neuroprotective effects.[31] It has antioxidant and neuroprotective effects. Oxidative stress is mainly mediated through overproduction of peroxides and depletion of antioxidants, and iron death/oxidation is characterized by lipid peroxidation and glutathione depletion, and at the molecular level, oxidative stress and iron death/oxidation processes overlap and share common molecular targets[32] . Many studies have shown that inflammation can induce disturbances in iron homeostasis[33] TNF-α is a pro-inflammatory cytokine, and high levels of ROS can activate NF-κB signaling downstream of TNF-α, which is essential in the regulation of immune and inflammatory processes.[34] . Therefore, there may be a relationship between iron death and oxidative stress and inflammation. As a natural product, amelioration of oxidative stress and inflammation production by angelica and danshen is an important mechanism of action of its active ingredients. Tanshinone iia can inhibit the secretion and expression of pro-inflammatory factors released from activated glial cells by inhibiting the RAGE/NF-κB signalling pathway[35] . Lignanserin can mediate Nrf2 activation to enhance antioxidant capacity and reduce ROS production, as well as modulate NF-κB, MAPK and JAK/STST signalling pathways to regulate different pro-inflammatory cytokines, including TLRs, TNF, IL-1, IL-6, etc.[36] The regulation of microRNAs, Leishmaniasis, PD-L1 expression and PD-1 checkpoint are all related to the immune response. In conclusion, the mechanism of action of Angelica sinensis and Salvia miltiorrhiza may be related to iron death, which needs to be further verified through extensive in vivo and ex vivo experiments.

5. Conclusions

Using a network pharmacology approach, this study illustrates the interactions between the active components, gene targets and signalling pathways involved in iron death in diabetic peripheral neuropathy, providing a new approach for the treatment of diabetic peripheral neuropathy. In this study, we found that Angelica sinensis and Salvia miltiorrhiza regulate the process of iron death against diabetic peripheral neuropathy through corresponding multiple gene targets and signaling pathways. A preliminary study on the mechanism of iron death regulation by Angelica sinensis and Salvia miltiorrhiza

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for the treatment of diabetic peripheral neuropathy in the future is still in need of extensive in vivo and ex vivo experimental validation.

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