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Mechanisms of Salvia miltiorrhiza and Angelica sinensis herbal pair in intervening ischemic stroke based on network pharmacology and molecular docking

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Abstract: *This study aims to explore the molecular mechanism of Salvia miltiorrhiza and Angelica sinensis (Salvia-Angelica) herbal pair in intervening ischemic stroke by network pharmacology method. The active ingredients and action targets of the Salvia-Angelica herbal pair were selected through TCMSP. Ischemic stroke disease targets were searched using the GeneCards, DisGeNET, and TTD databases. The Venny platform was used to intersect drug action targets with disease targets, obtaining potential action targets of Salvia-Angelica herbal pair for intervening ischemic stroke. The intersected targets were imported into the STRING database to construct a protein-protein interaction (PPI) network. Using the Cytoscape software, the visual graph of "Drug-Component-Target-Disease" and key targets PPI network were constructed. The DAVID database was used for GO enrichment and KEGG pathway enrichment analysis. Target-ingredient docking was verified and evaluated using CB-Dock2 platform. A total of 63 active ingredients of the Salvia-Angelica herbal pair were obtained, and 93 intersection targets of drugs and diseases were identified. Key active ingredients include luteolin, tanshinone IIA, dihydrotanshinlactone, β-sitosterol, etc. Core targets acting on the disease include AKT1, TNF, IL6, PTGS2, CASP3, EGFR, etc. GO enrichment resulted in 836 entries, suggesting that the Salvia-Angelica herbal pair functions in biological processes such as positive regulation of transcription from RNA polymerase II promoter, positive regulation of cell proliferation, and signal transduction. KEGG pathway enrichment resulted in 170 signal pathways, mainly involving Pathways in cancer, Lipid and atherosclerosis pathways, PI3K-AKT signaling pathways, and AGE-RAGE signaling pathway in diabetes complications, etc. Molecular docking showed that the active components from the Salvia-Angelica herbal pair exhibited better affinity with key targets. This study suggest that the Salvia-Angelica herbal pair exert its therapeutic effect on ischemic stroke through multiple components, multiple targets, and multiple pathways, including anti-inflammatory, antioxidant, anticoagulant effects, inhibiting cell apoptosis, promoting cell proliferation, and improving vascular endothelium.*

Keywords: *Salvia miltiorrhiza; Angelica sinensis; Herbal pair; Ischemic stroke; Network pharmacology; Molecular docking*

1. Introduction

Stroke is the leading cause of disability worldwide and the second leading cause of death. With the aging of the population, the incidence of stroke is continually rising. Additionally, the risk of stroke is also shifting to younger populations, further increasing the social burden [1]. Stroke can be categorized into ischemic stroke (IS) and intracerebral hemorrhage (ICH). Ischemic stroke, also known as cerebral infarction, refers to the interruption of cerebral arterial blood supply for various reasons, leading to local brain tissue hypoxia, ischemic necrosis or softening, and resulting in corresponding neurological deficits [2]. IS is the primary type of stroke, accounting for approximately 70% of all strokes [3]. It is characterized by high incidence, high mortality, high recurrence rate, and high disability rate [4]. Traditional single-ingredient Chinese medicines, compound prescriptions, and their formulations have

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multi-component, multi-target therapeutic characteristics and can be applied at various stages of IS onset. For instance, Salvia miltiorrhiza, Ligusticum wallichii, Astragalus mongholicus, and Angelica sinensis are commonly used single-ingredient Chinese medicines in traditional Chinese medicine treatment for IS [5]. The Salvia miltiorrhiza-Angelica sinensis herbal pair (Salvia-Angelica), commonly used in clinical practice, mainly treats syndromes of Qi and blood deficiency and Qi stagnation and blood stasis [6]. It has a favorable clinical application in the nervous system. The combined use of these two herbs exhibits superior free radical scavenging and antioxidant capabilities compared to using them individually [7]. This study selects the Salvia-Angelica herbal pair as a representative, employs network pharmacology and molecular docking methods to explore its target actions and pharmacological mechanisms in intervening IS, providing a reference basis for clinical and experimental research related to the treatment of IS with this herbal pair.

2. Materials and methods

2.1. Collection of active ingredients and their targets of Salvia-Angelica

Using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, https://tcmspw.com/tcmsp.php), we searched for the chemical components of Salvia miltiorrhiza and Angelica sinensis. Compounds with an oral-bioavailability (OB) of ≥30% and a drug-likeness (DL) of ≥0.18 were selected. The effective active ingredients of Angelica sinensis were supplemented with relevant literature. Using the "Related Targets" function of the TCMSP platform, the action targets of the drug active ingredients were searched. Using the Uniprot database (https://www.uniprot.org), protein names were corrected, and validated human (homo sapiens) genes were selected as effective drug targets.

2.2. Collection of disease targets related to IS

Using "ischemic stroke" and "cerebral infarction" as search terms, IS-related targets were obtained from Genecards (https://www.genecards.org), DisGeNET (https://www.disgenet.org), and TTD (https://db.idrblab.net/ttd). Data was integrated and deduplicated using Excel to obtain a comprehensive list of IS disease targets.

2.3. Selection of shared targets between drug active ingredients and disease

The previously obtained targets of drug active ingredients and disease targets were matched using the Venny 2.1.0 online platform (https://bioinfogp.cnb.csic.es/tools/venny/). Their intersection (i.e., shared targets between drug active ingredients and disease) was taken, and a Venn diagram was drawn.

2.4. Construction of the "Drug-Component-Target-Disease" network

The intersection targets selected in 2.3 and their corresponding active ingredients were imported into Cytoscape 3.10.0 software. Nodes represent drugs, active ingredients, targets, and diseases, while edges represent the relationship between two nodes. The "Drug-Component-Target-Disease" network was constructed, and the software's Analyzer Network tool was used to analyze network nodes, selecting potential key active components of Salvia-Angelica for intervening IS.

2.5. Construction of the protein-protein interaction (PPI) network

The intersection targets were imported into the STRING database (https://cn.string-db.org), limited to the human species, with a confidence level of 0.4. The protein-protein interaction (PPI) network and related data were obtained. The TSV file generated by the STRING database was imported into Cytoscape 3.10.0 software to construct a visualized PPI network and select key targets.

2.6. GO enrichment analysis and KEGG pathway analysis

Through the DAVID database (https://david.ncifcrf.gov/) we conducted gene ontology (GO) function enrichment and Kyoto encyclopedia of genes and genomes (KEGG) pathway enrichment analysis on the intersection targets. The relevant data is imported into the bioinformatics platform (https://www.bioinformatics.com.cn/) for visualization.

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2.7. Molecular docking verification

Select the drug active ingredients with higher node degree value and the key targets screened in the PPI network for molecular docking verification. The active ingredient of drug is ligand, and its chemical structure was downloaded from TCMSP and saved in "mol2" format. The key target protein is receptor, its 3D-structure was obtained from the RCSB PDB database (https://www.rcsb.org) and saved in "pdb" format. Structure based molecular docking was carried out on CB-Dock2 platform (https://cadd.labshare.cn/cb-dock2/php/index.php), and the binding site with the lowest Vina score was selected as the best docking mode [8]. The affinity of ligand and receptor reflects whether they can form a stable docking structure, it is generally believed that affinity value< -5 kcal/mol indicates that the docking structure is relatively stable, affinity value< -7.0 kcal/mol indicates strong docking conformation [9].

3. Results

3.1. Active components and action targets of Salvia-Angelica

From the TCMSP database, we retrieved and selected 59 active components of Salvia miltiorrhiza, corresponding to 137 action targets. For Angelica sinensis, 2 active components were found, and with the combination of literature reports [10-11], two more active components, Ligustilide and Ferulic Acid, were added, totaling 4 active components with 56 action targets. By merging the active components and their targets of the two herbs, a total of 63 active components and 150 action targets were obtained.

3.2. Potential action targets of Salvia-Angelica intervening IS

From the GeneCards database, 1881 disease targets for IS were selected. From the DisGeNET database, 1453 disease targets were obtained, and from the TTD database, 13 disease targets were found. After integrating and removing duplicates, 2808 targets were obtained. Through the Venny platform, the intersection of drug and disease targets was determined, resulting in 93 potential action targets (Figure 1).

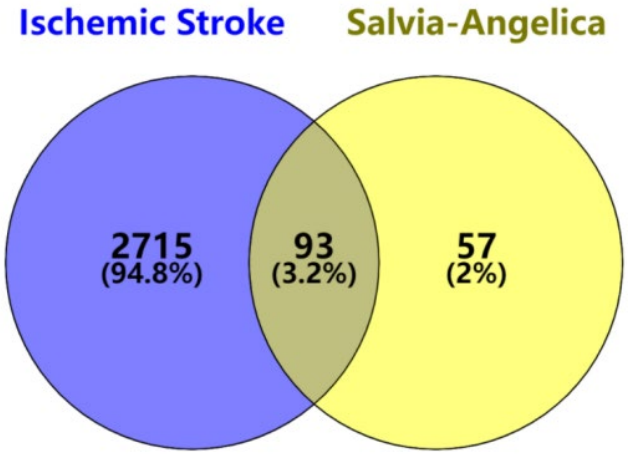

Figure 1: Venn diagram of potential targets for Salvia-Angelica intervention in IS

3.3. "Drug-Component-Target-Disease" network and key active components

We imported data related to drugs, active components, diseases, and intersection targets into the Cytoscape software, constructing a "Drug-Component-Target-Disease" network (Figure 2). Using the Analyzer Network tool to analyze network nodes and selecting based on node degree, we identified drug components with a larger number of target proteins (Table 1). This includes components like hesperidin, tanshinone IIA, dihydrotanshinlactone, and β-sitosterol, which might be the key active ingredients in Salvia-Angelica for intervening IS.

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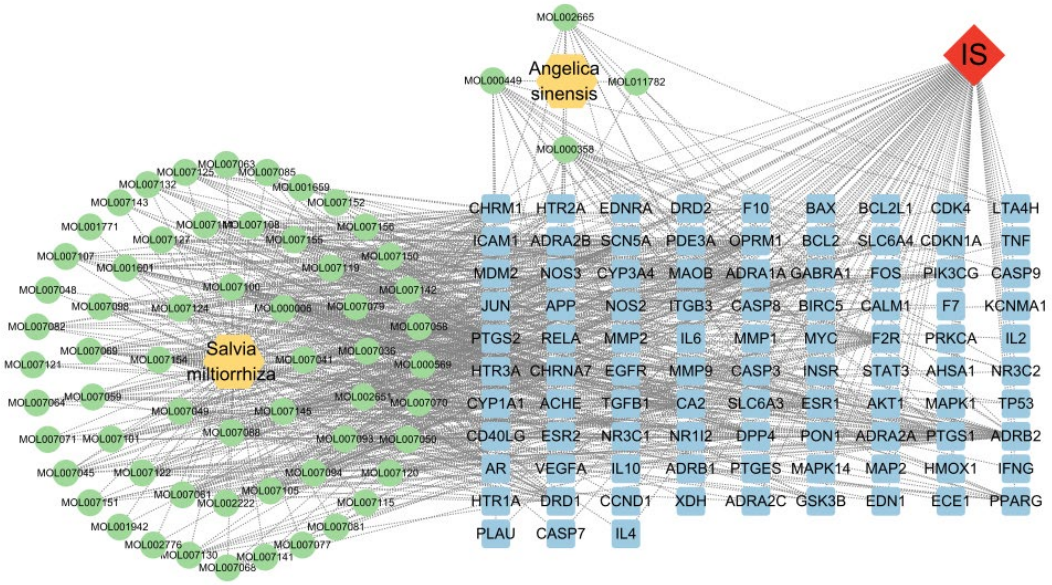

Figure 2: Drug-Component-Target-Disease network diagram

Table 1: Key active components of Salvia-Angelica for intervening IS (TOP15)

NO.	Source Drug	MOLID	Name of Active Component	Degree Value	OB (%)	DL
1	Salvia miltiorrhiza	MOL000006	luteolin	39	36.16	0.25
2	Salvia miltiorrhiza	MOL007154	tanshinone II A	29	49.89	0.4
3	Salvia miltiorrhiza	MOL007100	dihydrotanshinlactone	26	38.68	0.32
4	Angelica sinensis	MOL000358	beta-sitosterol	25	36.91	0.75
5	Salvia miltiorrhiza	MOL007145	salviolone	22	31.72	0.24
6	Salvia miltiorrhiza	MOL007049	4-methylenemiltirone	22	34.35	0.23
7	Salvia miltiorrhiza	MOL007041	2-isopropyl-8-methylphenanthrene-3,4-dione	21	40.86	0.23
8	Salvia miltiorrhiza	MOL007088	cryptotanshinone	20	52.34	0.4
9	Salvia miltiorrhiza	MOL007124	neocryptotanshinone II	19	39.46	0.23
10	Salvia miltiorrhiza	MOL007111	isotanshinone II	18	49.92	0.4
11	Salvia miltiorrhiza	MOL007108	isocryptotanshi-none	18	54.98	0.39
12	Salvia miltiorrhiza	MOL007093	dan-shexinkum d	18	38.88	0.55
13	Angelica sinensis	MOL000449	stigmasterol	17	43.83	0.76
14	Salvia miltiorrhiza	MOL007094	danshenspiroketallactone	17	50.43	0.31
15	Salvia miltiorrhiza	MOL002651	dehydrotanshinone II A	17	43.76	0.4

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3.4. Protein-Protein Interaction (PPI) network and key targets

Using the STRING database, 93 potential action targets of the Salvia-Angelica herbal pair for intervening IS were imported and a PPI network was constructed (Figure 3). This network includes 93 nodes, 1332 edges, and the average node degree is 28.6. The relevant data of the PPI network was further imported into the Cytoscape software. Based on the degree values, key targets were selected to construct the visualized PPI network of key targets, as shown in Figure 4, The larger the degree value, the more central the target position, the deeper the color, and the larger the diameter. This suggests that serine/threonine protein kinase 1 (AKT1), tumor necrosis factor (TNF), interleukin 6 (IL6), Prostaglandin G/H synthase 2 (PTGS2), Caspase-3 (CASP3), epidermal growth factor receptor (EGFR), estrogen receptor 1 (ESR1), and matrix metalloproteinase 9 (MMP9) are key targets.

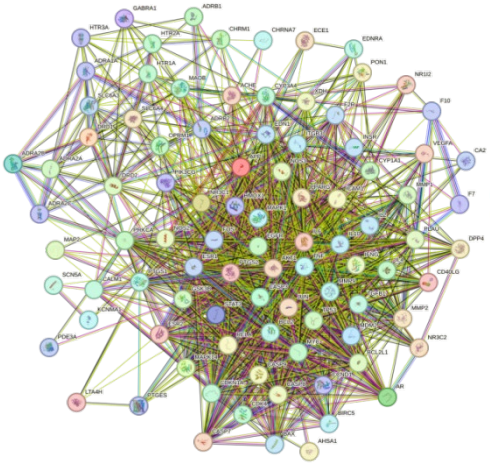

Figure 3: Protein-Protein Interaction (PPI) network

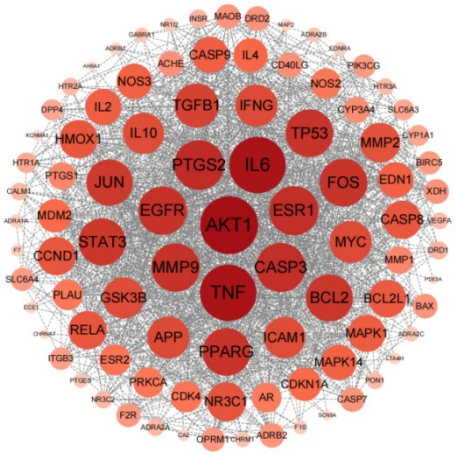

Figure 4: PPI network of key targets

3.5. GO enrichment analysis

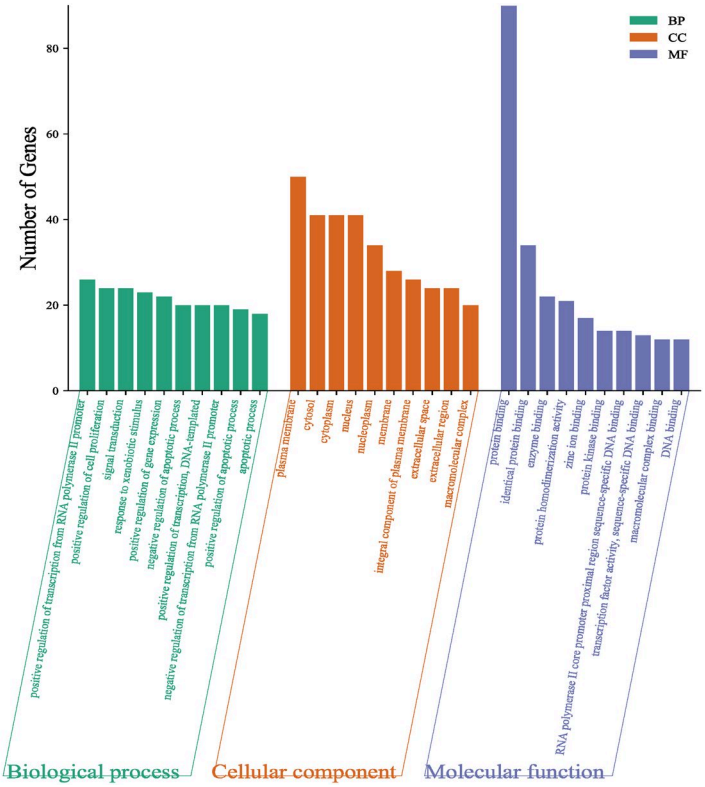

Figure 5: GO enrichment analysis (TOP 10) for the Salvia-Angelica herbal pair in intervening IS

Using the DAVID database, a GO enrichment analysis was conducted on the 93 potential action

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targets of the Salvia-Angelica herbal pair for intervening IS, resulting in 836 GO terms. This involves 657 terms for Biological Process (BP), 67 for Cellular Component (CC), and 112 for Molecular Function (MF). With a threshold of P<0.01, the top 10 GO terms were selected based on the Count value (i.e., the number of enriched target genes). The GO enrichment analysis bar chart was plotted using the bioinformatics platform, where the x-axis represents the GO term names and the y-axis represents the gene count values (Figure 5). The Biological Process mainly involves the positive regulation of transcription from RNA polymerase II promoter, positive regulation of cell proliferation, signal transduction, and regulation of the apoptotic process. Cellular Components mainly relate to the plasma membrane, cytosol, cytoplasm, and nucleus. Molecular Function primarily involves protein binding, identical protein binding, and enzyme binding. This indicates that the Salvia-Angelica herbal pair primarily intervenes the disease progression of IS through the above pathways and molecular mechanisms.

3.6. KEGG pathway analysis

Using the DAVID database, a KEGG pathway enrichment analysis was conducted on the 93 potential action targets of the Salvia-Angelica herbal pair for intervening IS, resulting in 170 signaling pathways. The 15 KEGG pathways with the smallest P-values were selected, and a KEGG pathway bubble chart was plotted using the bioinformatics platform. The x-axis represents the P-values, with smaller P-values indicating more significant pathways. The y-axis represents pathway names, and the size of the bubbles indicates the number of genes, with larger bubbles indicating more enriched targets in the signaling pathway (Figure 6). The KEGG pathway enrichment analysis shows that the significance levels of the "Pathways in cancer", "Lipid and atherosclerosis", and "AGE-RAGE signaling pathway in diabetic complications" are relatively high.

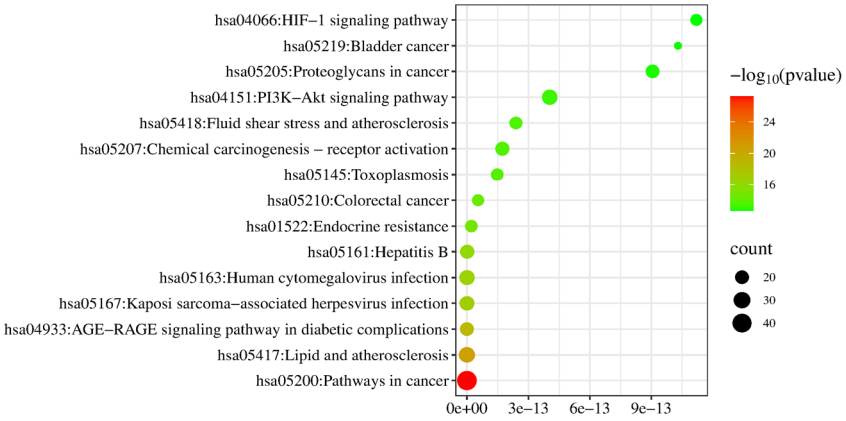

Figure 6: KEGG pathway analysis (TOP 15) for the Salvia-Angelica herbal pair in intervening IS

3.7. Molecular docking results

The 8 key targets with the largest degree values in the PPI network were selected, the corresponding target protein receptors were downloaded from the RCSB PDB database: AKT1 (PDB-ID 1H10), TNF (PDB-ID 1A8M), IL6 (PDB-ID 1ALU), PTGS2 (PDB-ID 5F19), CASP3 (PDB-ID 1CP3), EGFR (PDB-ID 1IVO), ESR1 (PDB-ID 1A52), MMP9 (PDB-ID 1GKD). The above 8 targets were docked with 15 key active components with large degree values (Table 1). The docking results are presented in Figure 7. The smaller the docking affinity value (i.e.,the bigger affinity absolute value), the better the docking structure of the target protein with the effective chemical components. We can draw the conclusion that each docking affinity value< -5 kcal/mol, the active component exhibited better affinity with key targets, particularly danshenspiroketallactone (MOL007094), dehydrotanshinone II A (MOL002651), dihydrotanshinlactone (MOL007100), tanshinone II A (MOL007154), with strong stability in the docking results. The docking mode of some receptors and ligands is shown in Figure 8, the molecular docking results indicate that the receptor and ligand have strong binding affinity.

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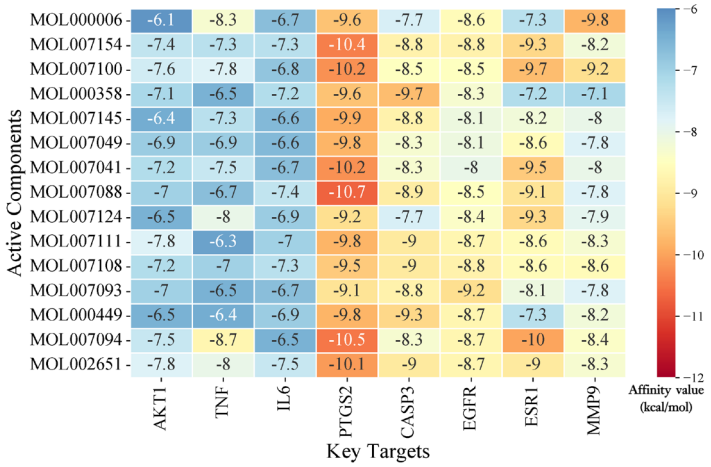
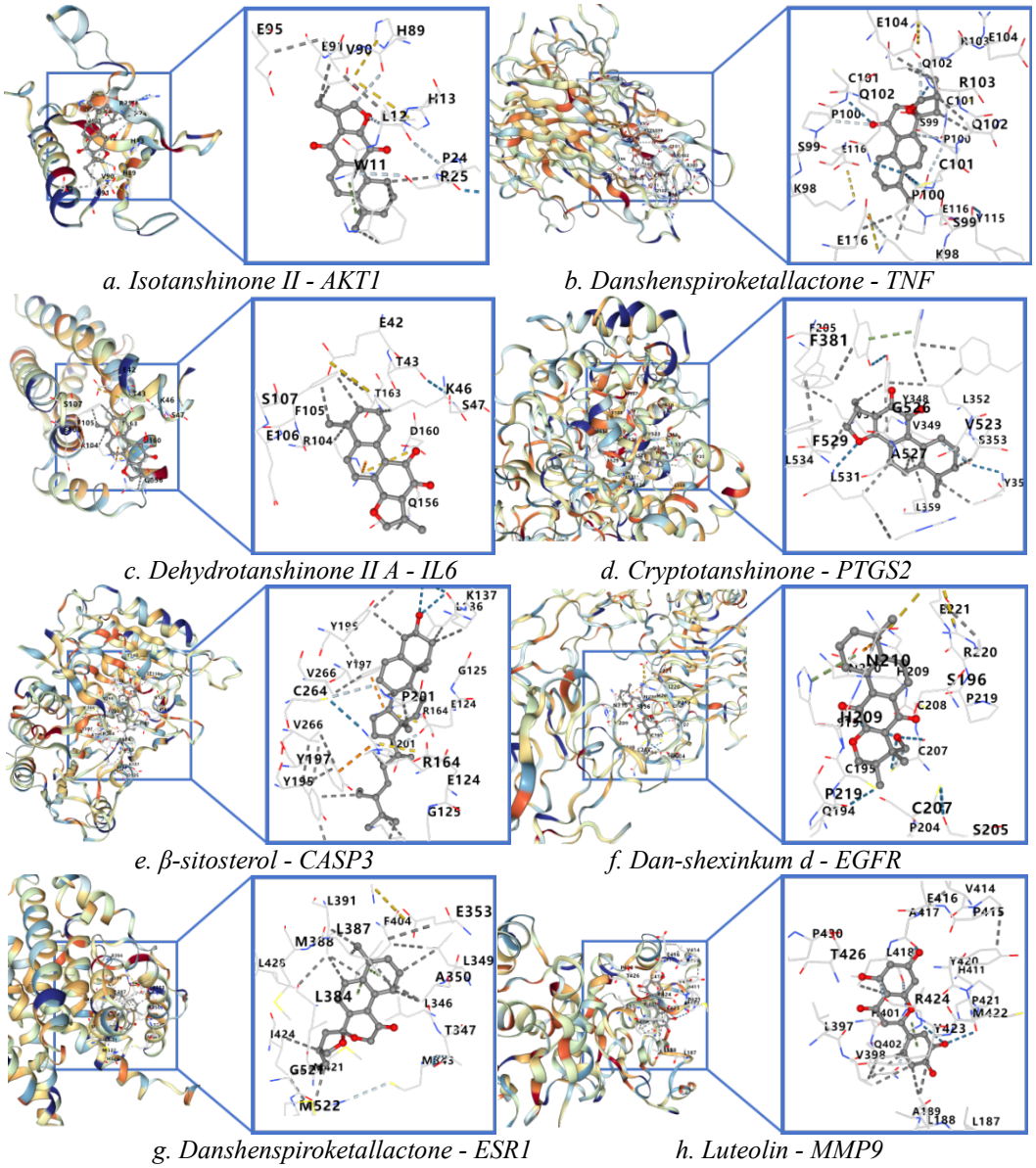


Figure 7: Heat map of docking affinity between active components and key targets



a. Isotanshinone II - AKT1 b. Danshenspiroketallactone - TNF

c. Dehydrotanshinone II A - IL6 d. Cryptotanshinone - PTGS2

e. β-sitosterol - CASP3 f. Dan-shexinkum d - EGFR

g. Danshenspiroketallactone - ESR1 h. Luteolin - MMP9

Figure 8: Molecular docking mode of some active components and key targets

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4. Discussion

In Traditional Chinese Medicine, IS (ischemic stroke) is categorized as "ZhongFeng, 中风", characterized by hemiplegia, crooked mouth and tongue, speech impairment, or sudden fainting and unconsciousness. The key pathogenesis of stroke is Qi deficiency and blood stasis, with obstruction in the cerebral collaterals. Blood stasis is crucial for the onset of IS, where stasis in the brain is termed stroke, and when in the limbs, it's called paralysis [12]. The brain is considered the residence of the vital spirit in traditional Chinese medicine. When the brain's collaterals are obstructed, impure blood cannot exit, and pure Qi cannot enter, leading to dysfunction of the brain marrow, which can result in neurological deficits in the body [13]. Salvia miltiorrhiza (Danshen) from the Labiatae family, the dried roots and rhizomes of Salvia miltiorrhiza Bge. *The Theory of Gynecology* (*Fu Ke Ming Li Lun*) believes that Salvia miltiorrhiza "nourishes and generates blood, more effective than angelica and rehmannia; regulates and stanches blood, is as potent as paeonia; disperses stagnation and generates new blood, twice as effective as ligusticum wallichii". *Compendium of Materia Medica* (*Ben Cao Gang Mu*) records Salvia miltiorrhiza as "dispelling stagnant blood and nourishing new blood", it's a key drug for promoting blood circulation and removing blood stasis. Angelica sinensis (Danggui) from the plant of Umbelliferae, the dried roots of Angelica sinensis (Oliv.) Diels, which nourishes and activates the blood, regulates menstruation and relieves pain. *The Retrospective Classic of Materia Medica* (*Ben Jing Feng Yuan*) records: "The medicinal properties of Angelica sinensis are sweet and warm, it harmonizes the nutritive blood, spicy and warm can disperse internal cold, allowing Qi and blood return to their places compatibly". When Salvia miltiorrhiza and Angelica sinensis are combined, one is cold and the other is warm, they promote blood circulation and remove stasis without harming the blood, which helps improve cerebral vascular obstruction.

The Salvia-Angelica herbal pair has 63 effective active ingredients identified. Through the "Drug-Component-Target-Disease" network, it's concluded that luteolin, tanshinone II A, dihydrotanshinlactone, β-sitosterol, etc. are the main effective ingredients of this combination for intervening IS. Luteolin is a flavonoid compound, in interventions against the MCAO rat model induced by middle cerebral artery occlusion, it was found that luteolin has antioxidant properties, reduces the area of cerebral infarction, inhibits neuronal apoptosis, and shows good neuroprotective effects [14]. GUO et al. [15] reported that luteolin can alleviate oxidative stress and inflammation by inhibiting the HIF-1α/NLRP3 signaling pathway, improving neurological deficits and cognitive impairments in MCAO rats. Tanshinone IIA is a diterpenoid quinone compound that promotes blood circulation and removes stasis, cools the blood and opens the collaterals, reduces damage to cerebral microvascular endothelial cells, and thus maintains the blood-brain barrier function [16]. Related research [17] shows that tanshinone IIA can activate the PI3K/Akt/mTOR pathway, increase the expression of phospholipid hydroperoxide glutathione peroxidase (GPX4) and cystine/glutamate transporter (SLC7A11) proteins, reduce the expression of prostaglandin G/H synthase 2 (PTGS2) proteins, significantly reverse the low expression of apoptosis regulator Bcl-2 (BCL2) and the high expression of apoptosis regulator BAX and Caspase-3, and inhibit the inflammatory response, ferroptosis, and apoptosis caused by ischemia-reperfusion. β-Sitosterol is a naturally bioactive steroidal compound with anti-inflammatory, antibacterial, antioxidant, antitumor, and lipid-lowering pharmacological effects. In terms of the nervous system, β-sitosterol can pass through the blood-brain barrier, deposit on the brain cell membrane, and promote cell proliferation and differentiation [18]. Research by GOGOI et al. [19] has shown that β-sitosterol has anticoagulant activity in vivo, can inhibit thrombin in a non-competitive manner, and promote thrombolysis. β-Sitosterol can also regulate the intestinal flora to inhibit the production of trimethylamine, reduce the levels of translation machinery-associated protein (TMA) and flavin-containing monooxygenase 3 (FMO3), improve cholesterol metabolism and atherosclerotic plaques, and enhance antioxidant capacity [20]. In addition, based on literature supplements, the active ingredients of Angelica sinensis, Ligustilide and Ferulic Acid, also have neuroprotective effects such as inhibiting oxidative stress, inhibiting cell apoptosis, anti-inflammatory, anti-platelet aggregation, and alleviating brain edema [21-22].

Protein-protein interaction (PPI) analysis shows that targets such as AKT1, TNF, IL6, PTGS2, CASP3, EGFR, etc., are closely related to the intervention mechanism of the Salvia-Angelica herbal pair for IS. AKT1 is one of the subtypes of protein kinase B with a wide tissue distribution, regulating cellular metabolism, proliferation, and angiogenesis. Deficiency of AKT1 induces endothelial cell dysfunction, reduces the migration and survival of vascular smooth muscle cells, leading to atherosclerosis and coronary artery occlusion [23]. TNF and IL6, as pro-inflammatory factors, participate in the inflammatory response in IS. When these pro-inflammatory factors are released into the blood, they can cause neuronal damage and disrupt the blood-brain barrier, exacerbating brain

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tissue edema [24]. IL6 has a dual role in the disease process of IS, acting as an inflammatory factor in the acute phase and as a neurotrophic agent in the sub-acute and recovery phases. It can stimulate the phosphorylation of signal transducer and activator of transcription 3 (STAT3) and the early transcriptional activation of genes related to angiogenesis, promoting increased angiogenesis and increased cerebral blood flow [25]. PTGS2, also known as COX2, acts as an inflammatory mediator in the inflammatory response. It can promote the increased expression of cyclic adenosine monophosphate (cAMP), increase the release of TNF and IL6, exacerbate post-brain injury inflammation, and expand the area of cerebral infarction [26]. Caspase-3 (CASP3) is referred to as an executor protease for apoptosis and is a common downstream element in various cell apoptosis pathways [27]. Effective inhibition of CASP3 activation can reduce neuronal apoptosis and improve brain neural function damage. EGFR is a member of the epidermal growth factor receptor family and is widely expressed in the central nervous system. Research by XU et al. [28] shows that EGFR can activate serine/threonine-protein kinase mTOR through the PI3K-AKT signaling pathway, promote protein synthesis, and regulate central neuron growth.

Based on the GO enrichment of key targets, Salvia-Angelica herbal pair mainly functions through the regulation of biological processes such as RNA transcription, cell proliferation, cell apoptosis, and signal transduction, as well as molecular functions like protein synthesis and enzyme binding, to exert its therapeutic effects on IS. KEGG enrichment indicates that the signaling pathways it involves mainly include Pathways in cancer, Lipid and atherosclerosis pathway, PI3K-AKT signaling pathway, and AGE-RAGE signaling pathway in diabetes complications, ect. Among them, the PI3K-AKT signaling pathway mainly regulates oxidative stress, inflammatory response, cell apoptosis, and other pathophysiological mechanisms involved in the disease process of IS [29]. The AGE-RAGE pathway mainly affects diabetic vascular complications and neuropathy [30], this pathway can activate nuclear factor kappa-B (NFKB), promote the expression of adhesion factors, endothelins, and pro-coagulation factors, enhancing the coagulation ability of endothelial cells. The binding of AGE and RAGE can also activate downstream signaling, such as the MAPK or PI3K pathways, which can lead to neuronal damage and apoptosis [30]. Abnormal lipid metabolism is one of the main risk factors for atherosclerosis (AS). The instability and rupture of AS plaques are the direct causes of thrombotic events [31]. AS is an important risk factor for IS, and the pathogenesis of both is closely related.

In summary, based on network pharmacology research, the active ingredients of Salvia-Angelica herbal pair that are effective in intervening ischemic stroke include luteolin, tanshinone II A, dihydrotanshinlactone, β-sitosterol, etc. They mainly act on target genes such as AKT1, TNF, IL6, PTGS2, CASP3, EGFR, and are involved in the regulation of Pathways in cancer, Lipid and atherosclerosis pathways, PI3K-AKT signaling pathways, and AGE-RAGE signaling pathway in diabetes complications. The primary effects of Salvia-Angelica herbal pair are promoting blood circulation, removing blood stasis, and nourishing the blood. It treats ischemic stroke through mechanisms such as inhibiting inflammatory responses, anti-oxidative stress, anti-platelet aggregation, inhibiting cell apoptosis, promoting cell proliferation, and improving endothelial function.

Acknowledgements

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