

Mechanism of Smilax china L. in the treatment of hepatic fibrosis based on network pharmacology and molecular docking technology

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Abstract:

Objective: To investigate the mechanism of the active ingredients of Smilax china L. in the treatment of hepatic fibrosis (HF).

Methods: The targets of the active ingredients of Smilax china L. were predicted using the TCMSP database, PubChem database, Babel software, Swiss Target Prediction platform, SEA platform, and UniProt database. The targets for HF were obtained using the DisGeNET database. Venn diagram platforms were used to intersect the active ingredients of Smilax china L. and HF targets. The key targets were selected using the STRING database to construct a protein-protein interaction network model. The key compounds were selected using the Cytoscape software to construct an active Smilax china L. ingredient-action target network. The intersection target was used for GO enrichment analysis and KEGG metabolic pathway analysis by ClueGO. The DockThor program was used to connect the important active ingredients and compounds of Smilax china L. with the corresponding intersection targets by calculating the binding energy and using the PyMOL software to create visual images.

Results: A total of 9 active ingredients, 209 targets, 56 targets, and 15 key targets related to HF were identified from Smilax china L. The biological processes associated with Smilax china L. for preventing HF mainly included collagen metabolism, positive regulation of vascular endothelial cell migration, muscle cell proliferation, and smooth muscle cell proliferation. The pathways mainly included the IL-17 signaling pathway, estrogen signaling pathway, prolactin signaling pathway, and pancreatic cancer pathway.

Conclusion: The mechanism of Smilax china L. in the treatment of HF was preliminarily explored. Smilax china L. has multi-component and multi-target characteristics, through which it can be used to treat HF.

Key words: network pharmacology, molecular docking, Smilax china L., hepatic fibrosis, mechanism.

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Abbreviations: HF, hepatic fibrosis; ECM, extracellular matrix; TCM, traditional Chinese medicine; OB, oral bioavailability; SMILES, Simplified molecular-input line-entry system; PPI, protein-protein interaction; MMPs, matrix metalloproteinases; VEGFs, Vascular endothelial growth factors.

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Introduction

Hepatic fibrosis (HF) is a pathological disorder in which a large amount of collagen-based extracellular matrix (ECM) is deposited when the liver yields a wound-healing response to various chronic stimuli; this diffuse deposition of various collagen in the liver results in destruction of the reticular structure of the basement membrane and capillarization of the hepatic sinusoids, eventually leading to formation and progression of fibrotic liver lesions. HF has been currently considered as an inevitable yet reversible early stage of hepatic cirrhosis and can progress to irreversible hepatic cirrhosis if not diagnosed and treated in time. Currently, there are no specific drugs for the clinical treatment of HF, and drugs for single-targeted therapies have marked side effects with low therapeutic efficacy. Statistics show that more than 1 million patients worldwide die every year from end-stage liver disease caused by HF [1, 2]. Therefore, it is of great importance to explore the applicability of traditional Chinese medicine (TCM) for preventing and treating HF, because TCM compound prescriptions or single prescriptions extends advantages, such as abundant active ingredients, numerous action targets, and diverse signaling pathways.

The TCM herb *Smilax china* L. has been gradually attracting attention from researchers owing to its advantages of large production, convenient collection, low price, and remarkable therapeutic effects. This study applied network pharmacology and molecular docking to construct a network of “active ingredient-potential target-action pathways” for exploring the multi-ingredient, multi-target, and multi-pathway characteristics of *Smilax china* L. in HF treatment and predict the potential HF targets and action mechanisms of *Smilax china* L. to establish a theoretical basis for further research. The research flow chart is shown in figure 1.

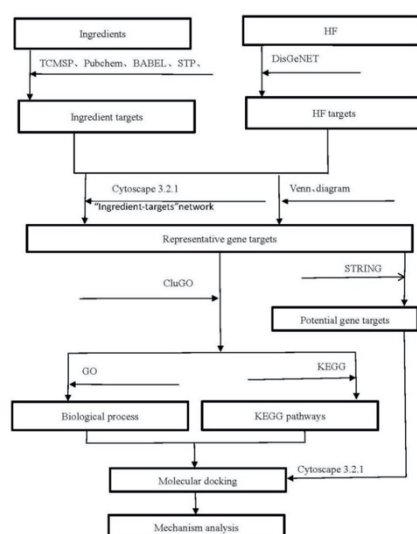


Figure 1. Research flow chart

Materials and methods

Database search and screening of the active ingredients of *Smilax china* L. and their targets

The active ingredients of *Smilax china* L. were screened using the TCMSP database (<http://tcmsp.w.com/tcmsp.php>) according to the following two absorption, distribution, metabolism, and excretion parameters: oral bioavailability (OB) of $\geq 30\%$ and drug-likeness of ≥ 0.18 . Simplified molecular-input line-entry system (SMILES) notations were searched with respect to the active ingredients in the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>). When no SMILES notation was found for a given active ingredient, the compound structure was imported into the Open Babel software for conversion to an SMILES notation, which was submitted to the platforms SwissTargetPrediction (<http://www.swisstargetprediction.ch/>) and SEA (<http://sea.bkslab.org/>) to predict and select targets with a probability of > 0 . Finally, the names of the selected target proteins were annotated using the Uniprot database (<http://www.uniprot.org/>).

Determination of the HF-related targets and prediction of potential therapeutic targets

The target genes of HF were obtained using the DisGeNET (v5.0) database (<https://www.disgenet.org/>). The DisGeNET database is a human disease-associated gene database containing 17,074 genes for 20,370 diseases with 561,119 gene-disease associations. The common targets of *Smilax china* L. and HF were computed using Venn diagrams (<http://bioinformatics.psb.ugent.be/webtools/Venn/>).

Construction of an ingredient-target network and screening of key active ingredients

The target genes of the active ingredients of *Smilax china* L. and HF were computationally mapped using a programming software, and the results were evaluated in Excel to establish the corresponding relationships between the ingredients and targets. The relationships were imported in the Cytoscape 3.2.1 software to construct a diagram of the active ingredient-target gene network, from which key components were selected according to topological parameters.

Construction of a protein-protein interaction (PPI) network and screening of key targets

The common targets of *Smilax china* L. and HF were imported into the STRING database (<https://string-db.org/>) for analysis after selecting humans as the species and setting the confidence threshold score to 0.7, a value high enough to ensure data reliability. Node 1 and node 2 in the analysis results were imported into the Cytoscape 3.2.1 software to construct a PPI network, which was subjected to topological analysis.

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The colors of the nodes varied gradually from yellow to red to reflect the degree of freedom from small to large values and help identify the key targets.

GO enrichment analysis and pathway analysis

GO enrichment analysis and KEGG pathway analysis were performed on the potential targets of *Smilax china* L. in the treatment of HF using the ClueGO plug-in of the Cytoscape 3.2.1 software while restricting the species to “human beings” and using *p*-values of ≤ 0.01 to indicate significant differences.

Molecular docking

The DockThor software was used to verify molecular docking of the target proteins with the highest degree of freedom in the PPI network to the important active ingredients of *Smilax china* L. screened using topological parameters (the active ingredients were excluded when the three-dimensional [3D] structures were unavailable in the PubChem database). The structures of the target proteins were obtained from the RCSB PDB protein structure database (<http://www.rcsb.org/pdb/home/home.do>), while the 3D structures of the active molecular compounds were obtained from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>). Molecular docking between the protein receptors and ligands was performed using the DockThor platform (<https://dockthor.lncc.br/v2/>), which reported the affinity. Larger the absolute value of the negative affinity, stronger the ligand-receptor docking. The results were imported into the PyMOL software for visual mapping analysis.

Results

Active ingredients and potential targets of *Smilax china* L.

Thirty-nine active ingredients of *Smilax china* L. were identified in the TCMSP database, which were further narrowed down to nine active ingredients with an OB of $\geq 30\%$ and drug-likeness of ≥ 0.18 (table 1). The targets of the nine active ingredients were narrowed down to 385 with a probability of > 0 , from which duplicate targets were removed, leaving 209 targets for further subsequent analysis.

HF-associated targets and potential treatment targets

As shown in figure 2, a total of 1,179 target genes of HF were obtained in the DisGeNET (v5.0) database, and a total of 56 common targets of the active ingredients of *Smilax china* L. and HF were obtained using the Venn diagram as follows: MMP2, MMP7, MMP13, MET, SERPINA6, ALOX5, HSD11B2, SMO, MAOA, SHBG, BCHE, ADORA2A, TACR1, PPARG, AHR, NR3C1, MAPK14, GC, MPO, F2, ARG1, NOX4, ESR1, DHCR7, VEGFA, SREBF2, GSK3B, MCL1, STAT1, MMP12, VDR, GLO1, PTPN1,

MMP3, PPARA, MMP8, PGF, PLA2G1B, MMP14, PIK3CG, epidermal growth factor receptor (EGFR), SYK, GPR35, F2R, NR1H4, PLG, INSR, ELAVL1, AKT1, SLC5A2, ABCC1, AKR1A1, PCSK7, CYP3A4, CBR1, and MMP9.

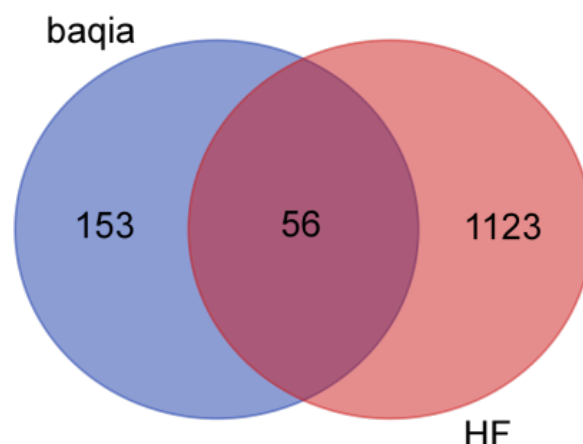


Figure 2. Venn diagram of the ingredients of *Smilax china* L. and the disease targets. HF, hepatic fibrosis

Construction of the ingredient-target network and screening of the key active ingredients

The ingredient-target network was first constructed using the Cytoscape software and then subjected to topological analysis using its plug-in Network Analyzer, with triangles representing active ingredients, circles representing targets, and colors gradually changing from yellow to red as the degree of freedom gradually increases, as shown in figure 3 and table 2.

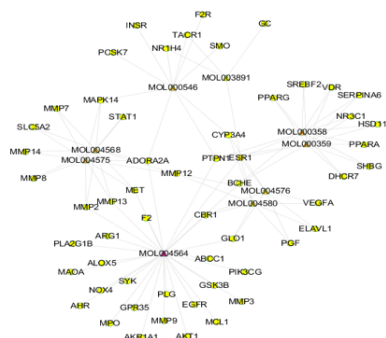


Figure 3. Ingredient-target network

Construction of the PPI network and screening of the key targets

The common targets were imported into the STRING database to obtain the interaction relationships between the target proteins as shown in figure 4 (nodes: 56, edges: 276, average node degree: 9.86, *p*-value: $< 1.0e-16$). The target proteins with high confidence were imported into the Cytoscape 3.2.1 software to generate a PPI network diagram, and an important sub-network was extracted (figure 5). The key targets were identified according to the topological parameters (table 3).

Table 1. Main active ingredients of Smilax china L.

MOL_ID	Molecule_name	Oral bioavailability	Drug-likeness
MOL000358	β -sitosterol	36.91390583	0.75123
MOL000359	Sitosterol	36.91390583	0.7512
MOL000546	Diosgenin	80.87792491	0.80979
MOL003891	Pseudoprotodioscin_qt	37.9306251	0.8738
MOL004564	Kaempferia	73.41080729	0.27069
MOL004567	Isoengelitin	34.65053943	0.69535
MOL004575	Astilbin	36.46195914	0.73628
MOL004576	Taxifolin	57.84156034	0.27345
MOL004580	Cis-dihydroquercetin	66.43699795	0.27344

Table 2. Topological parameters of the main ingredient nodes in the ingredient-target network

Ingredient	Molecular formula	Molecular Weight	Average shorter path length	Betweenness centrality	Closeness centrality	Degree
MOL004564	C ₁₆ H ₁₂ O ₆	300.26 g/mol	1.96875	0.64084428	0.50793651	29
MOL000359	C ₂₉ H ₅₀ O	414.7 g/mol	2.71875	0.1328812	0.36781609	12
MOL000358	C ₂₉ H ₅₀ O	414.7 g/mol	2.71875	0.1328812	0.36781609	12
MOL004575	C ₂₁ H ₂₂ O ₁₁	450.4 g/mol	2.9375	0.093115	0.34042553	11
MOL004568	C ₂₁ H ₂₂ O ₁₀	434.4 g/mol	2.9375	0.093115	0.34042553	11
MOL000546	C ₂₇ H ₄₂ O ₃	414.6 g/mol	2.5625	0.19181075	0.3902439	10
MOL004580	C ₁₅ H ₁₂ O ₇	304.25 g/mol	2.625	0.07152089	0.38095238	8
MOL004576	C ₁₅ H ₁₂ O ₇	304.25 g/mol	2.625	0.07152089	0.38095238	8
MOL003891	C ₂₇ H ₄₂ O ₃	414.6 g/mol	2.96875	0.04998937	0.33684211	4

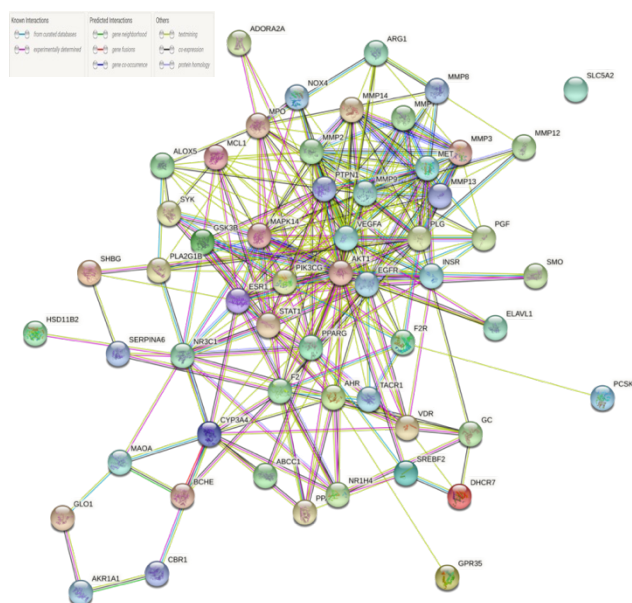
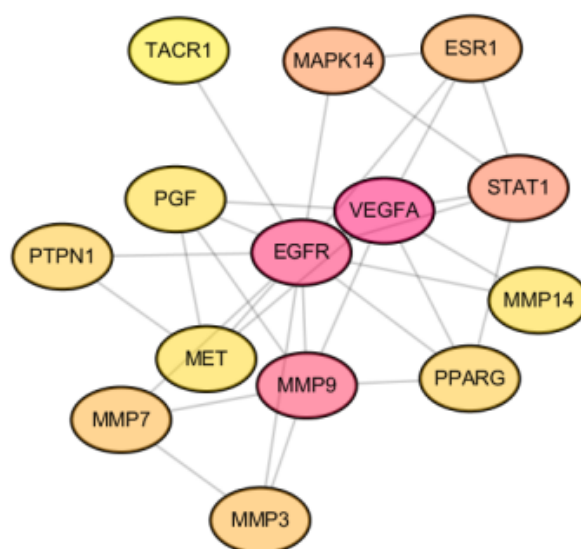
**Figure 4.** Protein-protein interaction network of potential targets**Figure 5.** Subnetwork of the key targets in the protein-protein interaction network

Table 3. Topological parameters of the target nodes in the subnetwork of the protein-protein interaction network

Gene name	Average shorter path length	Betweenness centrality	Closeness centrality	Degree
VEGFA	2.06521739	0.26266919	0.48421053	16
EGFR	2.17391304	0.22360989	0.46	13
MMP9	2.23913043	0.145798	0.44660194	12
STAT1	2.23913043	0.09078712	0.44660194	9
MAPK14	2.47826087	0.13557431	0.40350877	8
ESR1	2.32608696	0.05026262	0.42990654	7
MMP7	2.7826087	0.00256382	0.359375	6
MMP3	2.7826087	0.00256382	0.359375	6
PTPN1	2.80434783	0.0152634	0.35658915	5
PPARG	2.47826087	0.0980615	0.40350877	5
PGF	2.67391304	0.00116172	0.37398374	4
MET	2.7173913	0.00216318	0.368	4
MMP14	2.73913043	0.00113767	0.36507937	4
TACR1	2.93478261	0.09671498	0.34074074	3

Table 4. Molecular docking of the ingredients of Smilax china L. to the targets

MOL_ID	Molecule_name	Target	PDB ID	Affinity/kJ·mol ⁻¹
MOL004564	Kaempferid	VEGFA	4kzn	-7.368
		EGFR	4hjo	-9.414
MOL000359	Sitosterol	VEGFA	4kzn	-7.883
		EGFR	4hjo	-8.559
MOL000358	β-sitosterol	VEGFA	4kzn	-7.518
		EGFR	4hjo	-8.023
MOL004575	Astilbin	VEGFA	4kzn	-7.033
		EGFR	4hjo	-8.402
MOL004568	Engelitin	VEGFA	4kzn	-7.061
		EGFR	4hjo	-7.407
MOL000546	Diosgenin	VEGFA	4kzn	-7.535
		EGFR	4hjo	-9.213
MOL004580	Cis-dihydroquercetin	VEGFA	4kzn	-7.179
		EGFR	4hjo	-8.079
MOL004576	Taxifolin	VEGFA	4kzn	-6.125
		EGFR	4hjo	-7.382
MOL003891	Pseudoprotodioscin_qt	VEGFA	4kzn	-7.684
		EGFR	4hjo	-8.984

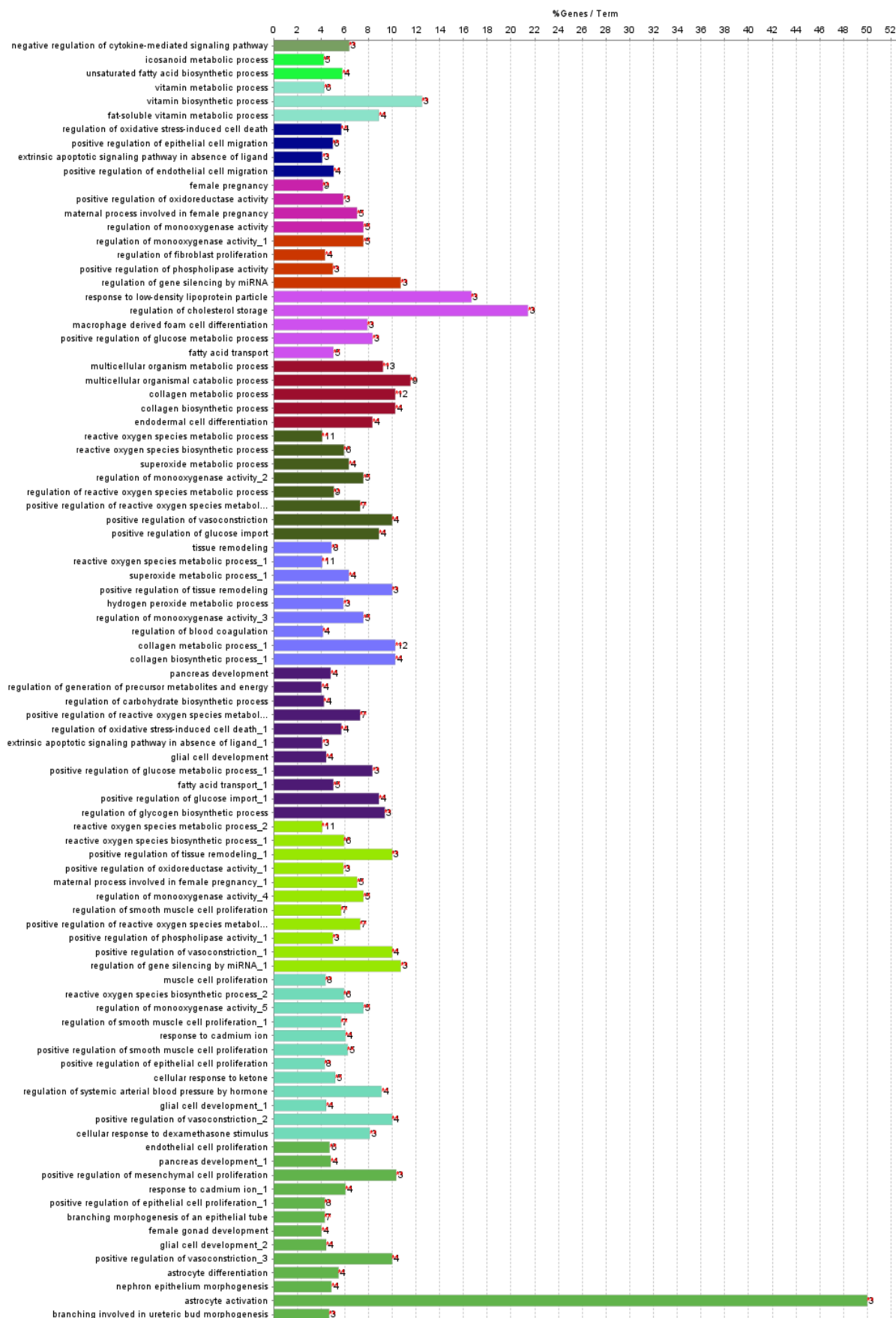


Figure 6. Enriched GO biological process

GO enrichment analysis and pathway analysis

The 56 target genes were imported into the ClueGO plug-in of the Cytoscape software for GO enrichment analysis and KEGG pathway analysis while restricting the species to “human beings” and using *p*-values of ≤ 0.01 to indicate significant differences. The GO enrichment analysis revealed the following 14 biological processes: collagen metabolic process, female pregnancy, eicosanoid metabolic process, multicellular organism metabolic process, muscle cell proliferation, negative regulation of the cytokine-mediated signaling pathway, positive regulation of epithelial cell migration, positive regulation of epithelial cell proliferation, positive regulation of reactive oxygen species metabolic process, reactive oxygen species metabolic process, regulation of cholesterol storage, regulation of monooxygenase activity, regulation of smooth muscle cell proliferation, and vitamin metabolic process (figure 6). The KEGG pathway analysis revealed the following six pathways: adherens junction, IL-17 signaling pathway, phospholipase D signaling pathway, prolactin signaling pathway, proteoglycans in cancer, and Rap1 signaling pathway (figure 7).

Molecular docking

The first two most important proteins in the PPI network, VEGFA (PDB ID: 4kzn), and EGFR (PDB ID: 4hjo) [3], were subjected to molecular docking verification with the active ingredients of *Smilax china* L. (table 4). Negative affinity indicates that the ligand molecules can spontaneously bind to the receptor proteins. In particular, the larger the absolute value of the negative affinity, the stronger the ligand-receptor docking, with affinity less than $-5.0 \text{ kJ} \cdot \text{mol}^{-1}$ indicating strong docking [4]. The verification results were visualized using the PyMOL software (Supplemental figure 1): (1) The yellow dotted lines represent hydrogen bonds; (2) small sticks marked by uppercase English letters with Arabic numerals around ligand molecules represent amino acids; (3) the red sticks of the ligand structure represent oxygen, and the blue sticks, carbon; (4) the hydrogen-bonded amino acids are labeled in red; (5) and the amino acids that cannot

be clearly displayed are thickened while blurring the background by 20–80% and coloring some protein bands, so as to facilitate observation. The virtual molecular docking revealed that the compounds were stably situated in the docking pockets. Kaempferia docked to VEGFA through hydrogen bonding with the two amino acids GLU-55 and CYS-45 near the active site and to EGFR through hydrogen bonding with amino acid MET-87 near the active site. Sitosterol docked to VEGFA through hydrogen bonding with the two amino acids GLU-61 and HIS-87 near the active site and to EGFR through hydrogen bonding with the two amino acids ASP-131 and ARG-135 near the active site. β -sitosterol docked to VEGFA through hydrogen bonding with amino acid GLU-26 near the active site and to EGFR through hydrogen bonding with the two amino acids ASP-149 and LYS-39 near the active site. Astilbin docked to VEGFA through hydrogen bonding with the four amino acids GLU-26, GLU-61, ARG-44, and CYS-56 near the active site and to EGFR through hydrogen bonding with the three amino acids ASP-149, MET-87, and ASN-136 near the active site. Engelitin docked to VEGFA through hydrogen bonding with the four amino acids GLU-26, GLU-61, ARG-44, and CYS-56 near the active site and to EGFR through hydrogen bonding with the four amino acids ASP-149, ASP-91, ASN-136, and LYS-39 near the active site. Diosgenin docked to VEGFA and EGFR through hydrogen bonding with amino acids GLU-18 and LYS-169 near the active site, respectively. Cis-dihydroquercetin docked to VEGFA through hydrogen bonding with the two amino acids GLU-18 and THR-65 near the active site and to EGFR through hydrogen bonding with the four amino acids ASP-149, MET-87, ASN-136, and LYS-39 near the active site. Taxifolin docked to VEGFA through hydrogen bonding with the two amino acids GLU-26 and GLU-61 near the active site and to EGFR through hydrogen bonding with the three amino acids ASP-149, ASP-94, and ASN-136 near the active site. Pseudoprotodioscin_{qt} docked to VEGFA through hydrogen bonding with the two amino acids HIS-87 and GLU-61 near the active site and to EGFR through hydrogen bonding with the two amino acids ASP-131 and ARG-135 near the active site.

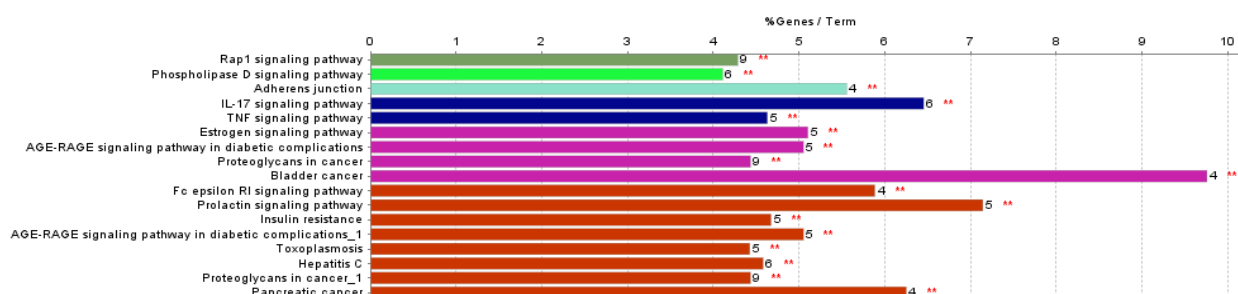


Figure 7. Enriched KEGG pathways of potential targets

Discussion

Smilax china L., also known as Jingangteng in China, is a member of the lily family; its dry rhizome is used as a traditional Chinese herbal medicine. It has a flat nature with a sweet and sour taste and acts on the liver and kidney meridian. *Smilax china* L. is effective in relieving dampness and wind and paralysis and pain, removing toxins and turbidity, invigorating blood circulation, and dispersing blood stasis. Modern pharmacological studies have shown that the main active ingredients of *Smilax china* L. responsible for its pharmacological effects are steroidal saponins, flavonoids, phenols, glycosides, stilbenes, and organic acids, all of which jointly make *Smilax china* L. yield anti-cancer, anti-inflammatory, anti-oxidant, and hypolipidemic properties [5]. Studies have shown that the flavonoids of *Smilax china* L. can effectively inhibit the two signal pathways of extracellular regulatory protein kinase and TGF- β -Smad2/3, thereby inhibiting the phosphorylation of extracellular regulatory protein kinase and Smad2/3 protein, consequently alleviating uterine fibrosis and increasing the content of matrix metalloproteinases (MMPs) in the uterine tissue to achieve therapeutic efficacy for pelvic inflammation [6]. Our study findings are consistent with the anti-HF mechanism of *Jiaweisinisan* revealed in our previous research [7-9]. Herein, we identified nine active ingredients of *Smilax china* L. through network pharmacology, namely Kaempferia, sitosterol, β -sitosterol, astilbin, engelitin, diosgenin, cis-dihydroquercetin, taxifolin, and pseudoprotodioscin_qt, that may be useful in the treatment of HF and show biological activities, such as anti-hepatic fibrosis, anti-inflammation, and immunoregulation.

As shown in the PPI network, VEGFA, EGFR, MMP9, STAT1, MAPK14, ESR1, MMP7, MMP3, PTPN1, PPARG, PGF, MET, MMP14, and TACR1 may be the key targets of *Smilax china* L. in the treatment of HF. Vascular endothelial growth factors (VEGFs) are a special type of cytokine for endothelial cells, secreted and produced by normal liver cells. They need to bind to receptors before exerting their biological activity. The main members of the VEGF family include VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor. VEGFA, also known as vascular permeability factor, is a potent and diffusible endothelial-specific mitogen that is released in hypoxic conditions and binds to the VEGF receptor expressed by the vascular endothelium, causing conformational changes in the tight junctions of vascular endothelial cells, leading to increased vascular permeability and enhanced angiogenesis [10, 11]. The activation process of hepatic stellate cells depends on the high expression of VEGFs and their receptors VEGF1 and VEGF2 [12]. Studies have shown that blood-activating and

stasis-dispersing TCM herbs play a bidirectional regulatory role in anti-HF. During the course of HF, such herbs can down-regulate the expression levels of VEGFA and EFGF to stop the occurrence and progression of HF; during the recovery period of HF, they up-regulate the expression levels of VEGFA and EFGF, playing a role in treating and reversing HF [13]. EGFR is a member of the human epidermal growth factor receptor family and is widely distributed on the surface of mammalian epithelial cells, fibroblasts, glial cells, and keratinocytes, with its signaling pathway playing an important role in the growth, proliferation, and differentiation of cells. EGFR mutation leads to continuous activation of the EGFR signaling pathway, which leads to abnormal cell proliferation. MMP is a calcium- or zinc-dependent extracellular proteolytic enzyme playing an important role in degrading and remodeling the ECM under various physiological and pathological conditions; in particular, MMP9 is related to multiple functions of endothelial cells, including their proliferation, differentiation, and migration [14].

The GO enrichment analysis revealed that *Smilax china* L. may exert an anti-fibrotic and proliferation-regulating effect in the treatment of HF through biological processes, such as regulation of collagen metabolism, positive regulation of vascular endothelial cell migration, regulation of muscle cell proliferation, and regulation of smooth muscle cell proliferation. The KEGG enrichment analysis revealed that the key targets of the PPI network were mainly enriched in the IL-17 signaling pathway, estrogen signaling pathway, prolactin signaling pathway, and pancreatic cancer pathway. IL-17 is mainly produced by helper T cells. The IL-17 signaling pathway regulates the expression of IL-6, IL-8, ICAM-1, and VEGF to promote the proliferation and migration of vascular endothelial cells and induce capillary lumen formation [15]. Therefore, it is speculated that *Smilax china* L. exerts a therapeutic effect on HF by regulating VEGFA, EGFR, MMP9, and other key targets through the IL-17 signaling pathway. The molecular docking analysis revealed that the affinity of Kaempferia, sitosterol, β -sitosterol, astilbin, engelitin, diosgenin, cis-dihydroquercetin, taxifolin, and pseudoprotodioscin_qt to VEGFA and EGFR was all less than $-5.0 \text{ kJ} \cdot \text{mol}^{-1}$. The larger the absolute value of the negative affinity, the stronger the ligand-receptor docking and the higher the possibility for the ligand molecule to be a potential active ingredient for HF treatment.

In summary, network pharmacology and molecular docking verified that *Smilax china* L. can inhibit fibrosis and inflammatory response and regulate immunity in the treatment of HF through a multi-ingredient, multi-target, and multi-pathway synergistic mode. The network pharmacology and molecular docking data can be experimentally verified in future research to provide a more solid theoretical

support for TCM treatment of HF.

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