The Mechanism of Compound Danshen Dripping Pills in the Treatment of Diabetic Retinopathy Based on Network Pharmacology and Molecular Docking

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Research

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Abstract

Background

Our previous randomized, double-blind, placebo-controlled, multi-center clinical study showed that Compound Danshen Dripping Pills (CDDP) had a significant and safe effect in the treatment of diabetic retinopathy (DR), but its mechanism is still unclear, which we would explain based on network pharmacology and molecular docking.

Method

The active ingredients of CDDP (composed of *Panax notoginseng, Salvia miltiorrhiza Bge.,* and *Borneol*) were searched in the TCMSP database. The validated target and Smiles number of the active ingredient are queried through the PubChem database, and the predicted target of the active ingredient is obtained through the Swisstarget Prediction database. The Drugbank, TTD, and DisGeNET databases were retrieved to obtain the related targets of DR. The core targets were obtained by the cluster analysis function of Cytoscape, and then the Protein-Protein Interaction was performed. The GO and KEGG signal pathways were enriched and clustered in David database. The potential active components and targets were docking with Autodock Vina, and the results were visualized by PyMOL.

Result

51 active components and 922 validation and prediction targets of CDDP, 715 targets of DR and 154 co-targets were obtained. Cluster analysis showed that there were two clusters, a total of 64 targets. Go and KEGG signal pathway enrichment analysis showed that the top 20 mainly included TNF and HIF-1 signaling pathway. In GO analysis, BP mainly includes positive regulation of smooth muscle cell proliferation and response to hypoxia, CC mainly includes extracellular space and extracellular domain, MF mainly includes protein binding and protein binding recognition. In KEGG database, the key genes in the TNF signaling pathway were TNF, NFkB and VEGF, in HIF-1 signaling pathway were the IL-6, STAT3, HIF1A and VEGF. Molecular docking results showed that all components of CDDP had a certain docking ability with TNF, NFkB, VEGF, IL-6, STAT3 and HIF1A, which of Asiatic acid and Salvianolic acid j was the strongest.

Conclusion

Based on the network pharmacology and molecular docking, the core active components of CDDP, mainly including Asiatic acid and Salvianolic acid j, which may play a role in regulating cell proliferation and response to inflammation and hypoxia by regulating the binding and recognition of intracellular and extracellular proteins, that is, mainly through TNF signaling pathway and HIF-1 signaling pathway.

1. Introduction

According to the data provided by the International Diabetes Federation, the number of diabetes mellitus (DM) patients in the world has reached 415 million, and by 2040, the total will exceed 600 million. Compared with simple hyperglycemia in the body, DM complications will bring greater economic burden and social burden. DM complications include macrovascular complications (such as cardiovascular disease, stroke) and microvascular complications (such as diabetic nephropathy, diabetic retinopathy (DR), and diabetic peripheral neuropathy). Among them, DR is a continuous process of microcirculation and continuous lesions. There are typical retinal microvascular lesions, including microangioma, hemorrhage, hard exudation, cotton wool plaque, venous bead-like changes, neovascularization, and fibrous tissue hyperplasia. According to the "Ophthalmology Clinical Guidelines" edited by the American Academy of Ophthalmology in 2006, DR is mainly divided into no obvious DR, non-proliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR), and DR often accompanied by diabetic macular edema (DME). The quality of life, psychology, and social behavior are affected to different degrees in patients with PDR, and more medical expenses are required (1). Vision loss occurs in the late stage of DME or PDR, and DR is one of the major causes of blindness in many countries (2). For the cause of DR, there are family inheritance, hyperglycemia, hyperlipemia, hypertension, etc. (3, 4). For the treatment of DR, the most important thing is to control blood sugar. Studies have shown that glycated hemoglobin 1c (HbAlc) is reduced by 10% on the original basis (such as 10% to 9%), and the incidence of DR is reduced by 43% (5). As demonstrated by the UKPDS, patients with tightly controlled blood pressure have a significant protective effect on the progression of DR (6). In Chinese patients with type 2 diabetes mellitus (T2DM), hyperlipidemia and high triglycerides are associated with an increased risk of DR (7). In the non-proliferative phase, the treatment is mainly based on oral drugs, including calcium dobesilate and intestinal kallikrein. In the severe stage of non-proliferative phase or proliferative phase, laser surgery is required, when with DME, Anti-Vascular endothelial growth factor (VEGF) is needed, such as ranibizumab. But real clinical studies show that the current treatment still has certain drawbacks, such as oral medicine are not suitable for all DR patients, and the effect is not good. For laser surgery, is a destructive treatment can only block the occurrence of blindness, but cannot improve the patient's vision, fundus lesions, although recent experiments have shown that laser treatment can actually improve the vision of some patients (8). After VEGF was injected, a relatively high proportion of patients (46%) may still require local or grid laser treatment (9). Therefore, the current treatment of DR is still defective.

We had enrolled 223 patients with non-proliferative diabetic retinopathy (NPDR) in a randomized, double-blind, placebo-controlled, multicenter clinical study with an intervention time of 24 weeks. The fundus fluorescein angiography results showed that the "excellent" and "effective" percentages of the high-dose and medium-dose Compound Danshen Dropping Pills (CDDP) group were 74% and 77%, respectively, which was significantly higher than the placebo group of 28% ($P < 0.001$). About the ophthalmoscopy, the "excellent" and "effective" percentages for the high-dose and medium-dose CDDP groups were 42% and 59%, respectively, significantly higher than the placebo group of 11% ($P < 0.001$), while without clinically significant adverse events. This clinical study demonstrates that CDDP has significant efficacy and safety in the treatment of NPDR (10). But now, the mechanism CDDP on DR is not clear.

Network pharmacology integrates multidisciplinary technologies and content such as systems biology, multi-directional pharmacology, computational biology, and network analysis, and conducts a multi-layer network of “disease-phenotype-gene-drug” to explore from a holistic perspective (11). Molecular docking is a method of drug design based on the characteristics of receptors and the interaction between receptors and drug molecules. It is a theoretical simulation method to study the interaction between molecules (such as ligands and receptors), and to predict their binding mode and affinity. Therefore, we want to explore the related mechanisms of CDDP (mainly composed of *Panax notoginseng (sanqi), Salvia miltiorrhiza Bge. (danshen),* and *Borneol (bingpian)*) in the treatment of NPDR through network pharmacology and molecular docking. (Figure 1)

2. Methods

2.1 Search and collection of active ingredients of CDDP

The active ingredients of the CDDP were searched using the TCMSP database (http://lsp.nwsuaf.edu.cn/tcmsp.php, Version: 2.3) (12). The search keywords were “sanqi”, “danshen” and “bingpian”, and according to the characteristics of pharmacokinetics, the oral bioavailability ≥ 30% and the drug-like ≥ 0.18 were set as screening conditions to obtain active ingredients.

2.2 Verified and Predicted targets of CDDP

Based on the active ingredients, the PubChem database (https://pubchem.ncbi.nlm.nih.gov/, 2019 Jan 8) was used to obtain the corresponding verification target and Smiles number (13). PubChem, the biological activity data of small organic molecules, is a database of chemical modules. Refers to a means of computer-simulated receptor binding to a ligand and predicting the affinity of both. Drug targets were predicted based on the ligand structure using SwissTarget Prediction (http://www.swisstargetprediction.ch) (14). First, the SMILES number of the active ingredient was collected from the PubChem database, and the calculation was performed using ALOGPS (http://www.vcclab.org/lab/alogps/, Version: 2.1) software which cannot directly obtain the Smiles number. First select the species "Homo sapiens" in the SwissTarget Prediction database, then enter the structure of the active ingredient and save the output file as a csv. format file.

2.3 Collection of DR related targets

Use "DR" as the search term by searching for TTD (15) (https://db.idrblab.org/ttd/, version date 20 JUN, 2019), DRUGBANK (16) (https://www.drugbank. Ca/, version date is 2017 Nov 8), DisGeNET (17) (http://www.disgenet.org/web/DisGeNET/menu/home, Version: 6.0) and remove duplicates.

2.4 Gene information standardization

The target information of the drugs and diseases that have been obtained is corrected in the Uniprot (https://www.uniprot.org/, 2019) database for genetic information(18). The Uniprot database is the most

informative and resource-rich protein database. Finally, a "drug-ingredient-target" network map was constructed using Cytoscape software (http://cytoscapeweb.cytoscape.org/, Version: 3.2.1) (19).

2.5 Cluster analysis of co-targets

The MCODE plug-in of Cytoscape 3.2.1 was used to cluster the common targets of CDDP and DR. The parameters: node score cutoff 0.2; k-core 4; max depth 100. Pass the core target through the STRING database (20) (https://string-db.org/, Version:11.0) Protein protein interaction (PPI) analysis was performed, Multiple protein was selected, target gene name was input, and Homo was selected as the species.

2.6 Signal pathway analysis

With DAVID database (https://david.ncifcrf. gov/summary. Jsp, Version 6.8), the core targets of CDDP and DR were analyzed by GO annotation, including biological process (BP), cell composition (CC) and molecular function (MF) and KEGG signaling pathways. The results are visualized with Omicshare (https://www.omicshare.com).

2.7 Molecular docking

In PDB database (http://www.rcsb.org/) to obtain the target gene protein, AutoDockTools was used to remove water molecules, hydrogenate and charge. The 2D structure of compounds were downloaded from PubChem database and opened by AutoDockTools to optimize the ligand. Autodock used semi flexible docking method to retain the docking results. The binding energy (kJ·mol-1) results were visualized by Prism 8. For the top three results of binding energy (kJ·mol-1), PyMOL file was used to visualize the results.

3. Results

2.1 Results of active ingredients of *Panax notoginseng, Salvia miltiorrhiza Bge.,* and *Borneol*

According to the qualification conditions, 6 active ingredients of *Panax notoginseng*, 42 active ingredients of *Salvia miltiorrhiza* and 3 active ingredients of *Borneol* were collected from TCMSP database. (Table 1)

Table 1 Active ingredients of CDDP

Chinese medicine	Compounds	OB (%)	DL	PubChem ID
Panax notoginseng	quercetin	46.43334812	0.27525	5280343
	beta-sitosterol	36.91390583	0.75123	222284
	Stigmasterol	43.82985158	0.75665	5280794
	Mandenol	41.99620045	0.19321	5282184
	ginsenoside rh2	36.31951	0.55868	119307
	ginsenoside f2	36.43175	0.25282	9918692
Salvia miltiorrhiza Bge.	tanshinone iia	49.88730004	0.39781	164676
	Tanshindiol B	42.66581049	0.45303	5321620
	tanshinaldehyde	52.4747043	0.45196	124268
	sugiol	36.11353486	0.27648	94162
	sclareol	43.67068458	0.2058	163263
	salviolone	31.72415039	0.23568	10355691
	Salvilenone	30.38365387	0.37639	389885
	salvianolic acid j	43.37604991	0.72497	24177556
	salvianolic acid g	45.56485578	0.60602	11530200
	przewaquinone f	40.30788399	0.45925	126073
	Przewaquinone E	42.85485204	0.45301	126072
	przewaquinone c	55.7416731	0.40408	126071
	Przewaquinone B	62.24005962	0.41374	622085
	przewalskin b	110.3240001	0.43809	16102114
	przewalskin a	37.10650066	0.64901	16090911
	Poriferasterol	43.82985158	0.75596	5281330
	poriferast-5-en-3beta-ol	36.91390583	0.75034	457801
	neocryptotanshinone ii	39.46299114	0.23157	15690458
	neocryptotanshinone	52.48799701	0.32306	389888
	Miltirone	38.75698635	0.25418	160142
	miltipolone	36.55611206	0.36803	10086184

	miltionone □	71.02970321	0.43711	51531511
	miltionone □	49.68439433	0.32125	53474332
	microstegiol	39.61229457	0.27734	403772
	Methylenetanshinquinone	37.07319368	0.36017	105118
	manool	45.04431636	0.20208	3034394
	luteolin	36.16262934	0.24552	5280445
	Isotanshinone II	49.91602574	0.39674	44425166
	isoimperatorin	45.46424674	0.22524	68081
	formyltanshinone	73.444622	0.41736	348675638
	epidanshenspiroketallactone	68.27315929	0.30549	102004791
	dihydrotanshinone□	45.04327919	0.36015	11425923
	digallate	61.84861803	0.25635	54711004
	Dehydrotanshinone II A	43.76228599	0.40019	128994
	Danshenol B	57.9508753	0.55764	3083515
	Danshenol A	56.96524899	0.52172	3083514
	cryptotanshinone	52.34196226	0.39555	160254
	C09092	36.06948986	0.2474	442027
	Baicalin	40.12360996	0.75264	64982
	4-methylenemiltirone	34.34867589	0.22726	14609851
	2-isopropyl-8-methylphenanthrene-3,4-dione	40.86015408	0.22897	135872
	1,2,5,6-tetrahydrotanshinone	38.74538672	0.35791	124416
Borneol	Asiatic acid	41.38281219	0.71097	119034
	Bronyl acetate	59.29526304	0.51159	93009
	Dipterocarpol	41.708061	0.76437	441676

2.2 CDDP-Compounds-Targets-DR Network

In TCMSP, there are 186 targets of *Panax notoginseng*, 215 targets of *Salvia miltiorrhiza Bge.*, and without validated targets for *Borneol*. There are 433 predict targets for *Panax notoginseng*, 2850 predict targets for *Salvia miltiorrhiza Bge.*, and 246 predict targets for *Borneol*. The ingredients of CDDP and their

corresponding targets were introduced into the Cytoscape software, and CDDP-Compunds-Targets-DR Network was drawn. (Figure 2)

2.3 Disease and drug target intersection results

Using MCODE cluster analysis, the results showed that there were two clusters A and B, a total of 64 targets, including ABCB1, ACE, AGTR1. Cluster A: score 26.486, nodes 38, edges 490. Cluster B: score 9.6, nodes 26, edges 490. (Figure 3)

The String database was used to display the interaction between proteins, in which the red line represents fusion evidence, the green line represents adjacent evidence, the blue line represents coexistence evidence, the purple line represents experimental evidence, the yellow line represents text mining evidence, the light blue line represents database evidence, and the black line represents Co expression evidence. The results show that, number of nodes: 64. number of edges: 1100. average node degree: 34.4. avg. local clustering coefficient: 0.769. expected number of edges: 276. PPI enrichment p-value: < 1.0e-16. (Figure 4)

2.4 Signal pathway enrichment results

According to the results obtained from DAVID database, the top 20 of KEGG pathway mainly include TNF signaling pathway and HIF-1 signaling pathway. In GO analysis, BP mainly includes positive regulation of smooth muscle cell proliferation and response to hypoxia, CC mainly includes extracellular space and extracellular domain, MF mainly includes protein binding and protein binding recognition. (Figure 5)

In KEGG database, we searched the TNF signaling pathway, HIF-1 signaling pathway and the key genes in the pathway, and preliminarily determined that TNF, NFkB and VEGF were the key genes in TNF signaling pathway, while IL-6, STAT3, HIF1A and VEGF were the key genes in HIF-1 signaling pathway. (Figure 6, 7)

2.5 Molecular docking results

In KEGG database, we preliminarily determined that TNF, NFkB and VEGF are the key genes in TNF signaling pathway, while IL-6, STAT3, HIF1A and VEGF are the key genes in HIF-1 signaling pathway. In this regard, we used 51 compounds from CDDP to obtain the 2D structures of 46 compounds in PubChem database, and docking with TNF, NFkB, VEGF, IL-6, STAT3, HIF1A molecules respectively.

Molecular docking results showed that all components of CDDP had a certain docking ability with TNF, NFkB, VEGF, IL-6, STAT3 and HIF1A, among which Asiatic acid (PubChem ID 119034) and Salvianolic acid j (PubChem ID 24177556) had the strongest docking ability (Figure 8). Among them, the first three substances docking with TNF were Asiatic acid, Ginsenoside f2 and Danshenol B. The first three substances docking with NFkB were Asiatic acid, Przewalskin b and Salvianolic acid j. The first three substances docking with VEGF were Asiatic acid, Ginsenoside f2, Salvianolic acid j. The first three substances docking with IL-6 were Asiatic acid, Danshenol B and Przewalskin b. The first three

substances docking with STAT3 were Asiatic acid, Ginsenoside f2 and Salvianolic acid j. The first three substances docking with HIF1A were Asiatic acid, Ginsenoside f2 and Salvianolic acid j. (Figure 9)

4. Discussion

At present, there are still shortcomings in the treatment of DR. The most important ones are early screening, early prevention, and early treatment. Studies have shown that early screening of DR by national organizations can reduce blindness by 30-50% (21). At the same time, the control of related risk factors can also reduce the blindness rate to a certain extent. Strict control of blood pressure, the risk of DR blindness can be reduced by 47% (22). However, current awareness of DR risk factors is still lacking, as current relevant risk factors are not applicable to all patients (23). For example, HbA1c may account for only 10% of the risk of DR. Blood pressure and serum total cholesterol may account for no more than 10% of the risk of DR (24). Family inheritance accounts for about 25-50% (25). In fact, studies have shown that some of the patients with poorly controlled blood glucose and/or blood pressure do not develop DR (26), while other patients with appropriate controls have severe stages of DR (27), indicating that other unknown risk factors are also playing an important role. For the pathogenesis of DR, including extracellular glutamate excitotoxicity, oxidative stress, loss of neurotrophic factors, and neuroinflammation, these factors then impair blood-retinal blockade and lead to up-regulation of pro-angiogenic growth factors and hormones that produce DME and PDR (28-30).

Through network pharmacology and molecular docking, we first found 51 active components of *Panax notoginseng*, *Salvia miltiorrhiza*. and *Borneol* contained in CDDP in the TCMSP database, and then searched the 922 targets and Smiles number of the active components through the PubChem database and Swisstarget Prediction database. 715 targets associated with NPDR were found in Drugbank, TTD, and DisGeNET databases. Through the analysis of GO and KEGG signaling pathways, the results showed that CDDP may play a role by regulating the binding and recognition of intracellular and extracellular proteins to regulate cell proliferation and response to inflammation and hypoxia, that is, mainly through TNF signaling pathway, and HIF-1 signaling pathway. The results of molecular docking showed that the core components of CDDP, including Asian acid (PubChem ID 119034) and Salvianolic acid j (PubChem ID 24177556), could play a role by regulating the biological functions of key genes in the two signaling pathways, such as TNF, NFkB, VEGF, IL-6, STAT3 and HIF1A.

Hyperglycemia is an important risk factor for the occurrence and development of DR, which can cause damage to retinal microvascular system, including capillary swelling and deformation, Blood retinal barrier (BRB) damage. In the environment of high glucose concentration, hyperglycemia leads to cell dysfunction, retinal vascular and nerve damage, structural defects and further damage of retinal cells, functional disorders (31-33). Ages binding to rage induce a strong intracellular signal transduction cascade, leading to endothelial dysfunction, key pro-inflammatory cytokines and pro angiogenic factors, such as tumor necrosis factor - α (TNF - α) and nuclear transcription factor - kB (NF -kb) Activation of NF - kb mediates pericyte apoptosis, vascular inflammation and angiogenesis, as well as the destruction of

endogenous BRB. The end result of all these events is damage to the neural and vascular components of the retina (32, 34-36).

Inflammation is very important for the pathogenesis of diabetes and metabolic syndrome. Chronic inflammation is the main event of type 1 diabetes and a typical symptom of type 2 diabetes, showing high levels of C-reactive protein (37-39). Diabetes itself could increase the release of retinal inflammatory mediators, such as interleukin-6 (IL-6) and TNF α. Inflammation is an important factor in the pathogenesis and development of DR. One of the most convincing evidence is from the study of patients with diabetic rheumatoid arthritis. The study showed that the incidence rate of DR in patients with rheumatoid arthritis treated with salicylate is low (40). NF - kB in the retina of diabetic patients was activated at the early stage of DR development, and its activity remained active even though the apoptosis process of retinal capillary cells was accelerated (41). NF - kB could initiate apoptosis in response to high glucose pressure in retinal pericytes, which may explain the early cell death in DR (42). At rest, microglia help maintain retinal tissue homeostasis by phagocytosis and controlling low-grade inflammation. However, the long-term tissue stress caused by hyperglycemia can lead to chronic inflammation due to the overreaction of microglia with the concomitant pro-inflammatory cytokines and chemokines (43).

Although all retinal cells rely on ATP as a fuel source, photoreceptors are the biggest consumers. Photoreceptors use more than 75% of retinal oxygen and contain more than 75% of retinal mitochondria. They produce large amounts of ATP through oxidative phosphorylation, which is necessary for light transduction (44). Retinal blood flow increases in response to light-induced neuronal activity, ensuring that retinal neurons receive adequate oxygen and nutrition as metabolic requirements change. In DR, this response is known as "functional hyperemia". Decreased functional hyperemia may lead to retinal hypoxia and the development of DR (45). If oxygen consumption rate is reduced and extracellular acidification is increased, cytochrome c would release and promote apoptosis, which indicates that mitochondrial dysfunction involved in structural changes can mediate the death of retinal vascular cells in DR (46, 47). Hypoxia can also lead to high expression of VEGF in pericytes, müller cells, astrocytes and retinal endothelial cells (31). VEGF stimulated endothelial cell proliferation and migration, and enhanced vascular permeability (48-50). The damage to endothelial cells and the loss of pericytes trigger the process of vascular lumen stenosis, thus reducing blood flow. This, in turn, exacerbates retinal ischemia and hypoxia. Long term studies have shown that HIF-1 α, an isoform of HIF, may play a key role in hypoxia. It can activate müller cells to form a chronic inflammatory environment and induce VEGF and fibroblast growth factor. The overexpression and accumulation of factor (FGF) and the binding of circulating VEGF with VEGF receptor on retinal vascular endothelial cells trigger the tyrosine kinase pathway (51), which leads to retinal fibrosis and pathological neovascularization (52-55).

In conclusion, the core active components of CDDP, mainly including Asiatic acid and Salvianolic acid j, may play a role by regulating the binding and recognition of intracellular and extracellular proteins to regulate cell proliferation and response to inflammation and hypoxia, that is, mainly through TNF

signaling pathway and HIF-1 signaling pathway to play a therapeutic role in DR. And we would verify our prediction mechanism through animal experiments or cell experiments.

Declarations

Ethics approval and consent to participate

Not Applicable

Consent for publication

Not Applicable

Availability of data and materials

Not Applicable

Author contributions

FML and XLT designed the protocol. DJ, LYD, RRZ, and YYD carried out the active ingredient, and relevant targets search. FML and XDA contributed to data extraction and results analysis. YRZ and SHZ corrected the related data. All authors approved the final version of the manuscript.

Competing Interests

There were no any of potential conflicts of interest of all authors.

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Figures

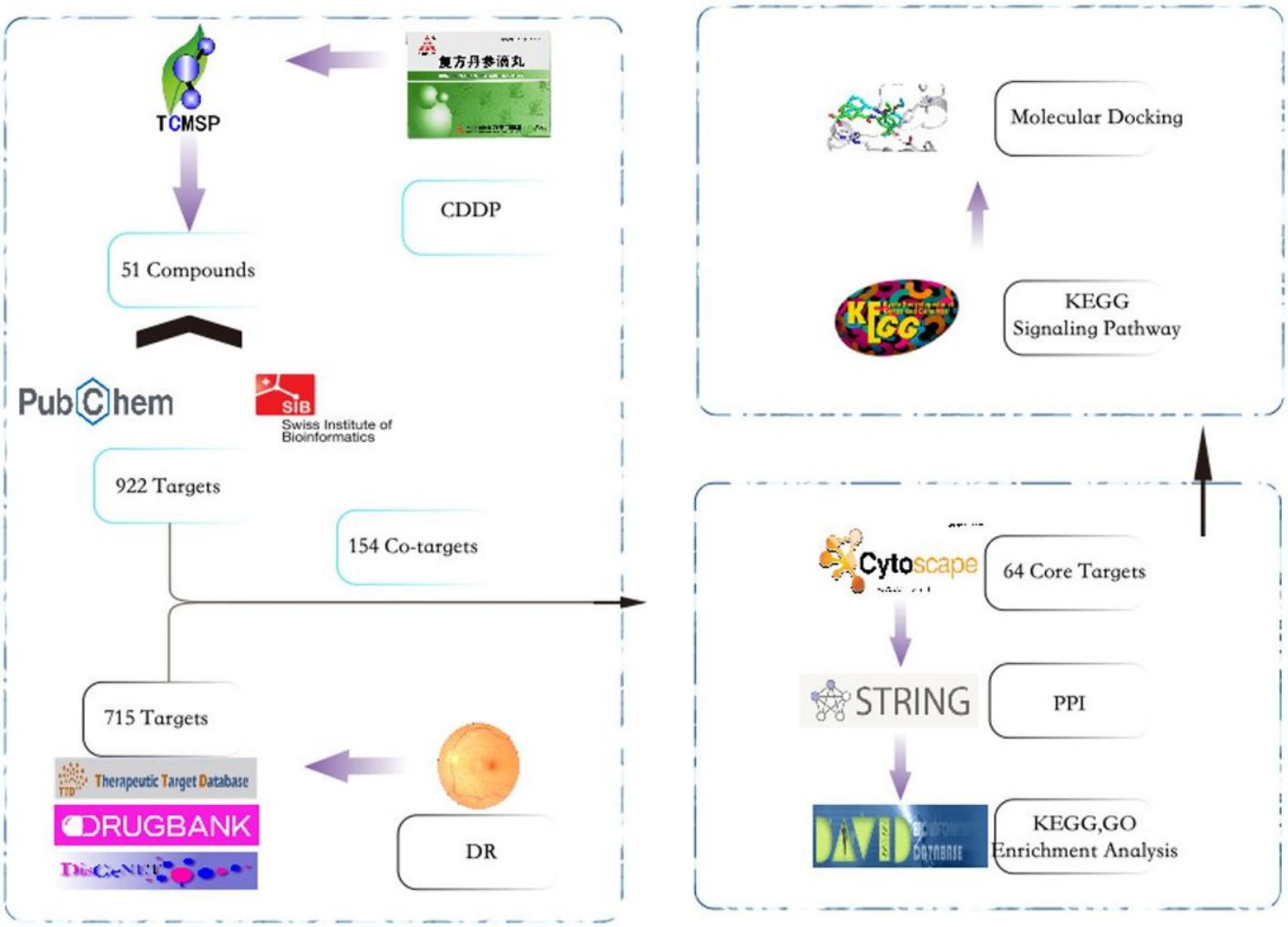

Figure 1

Flow chart

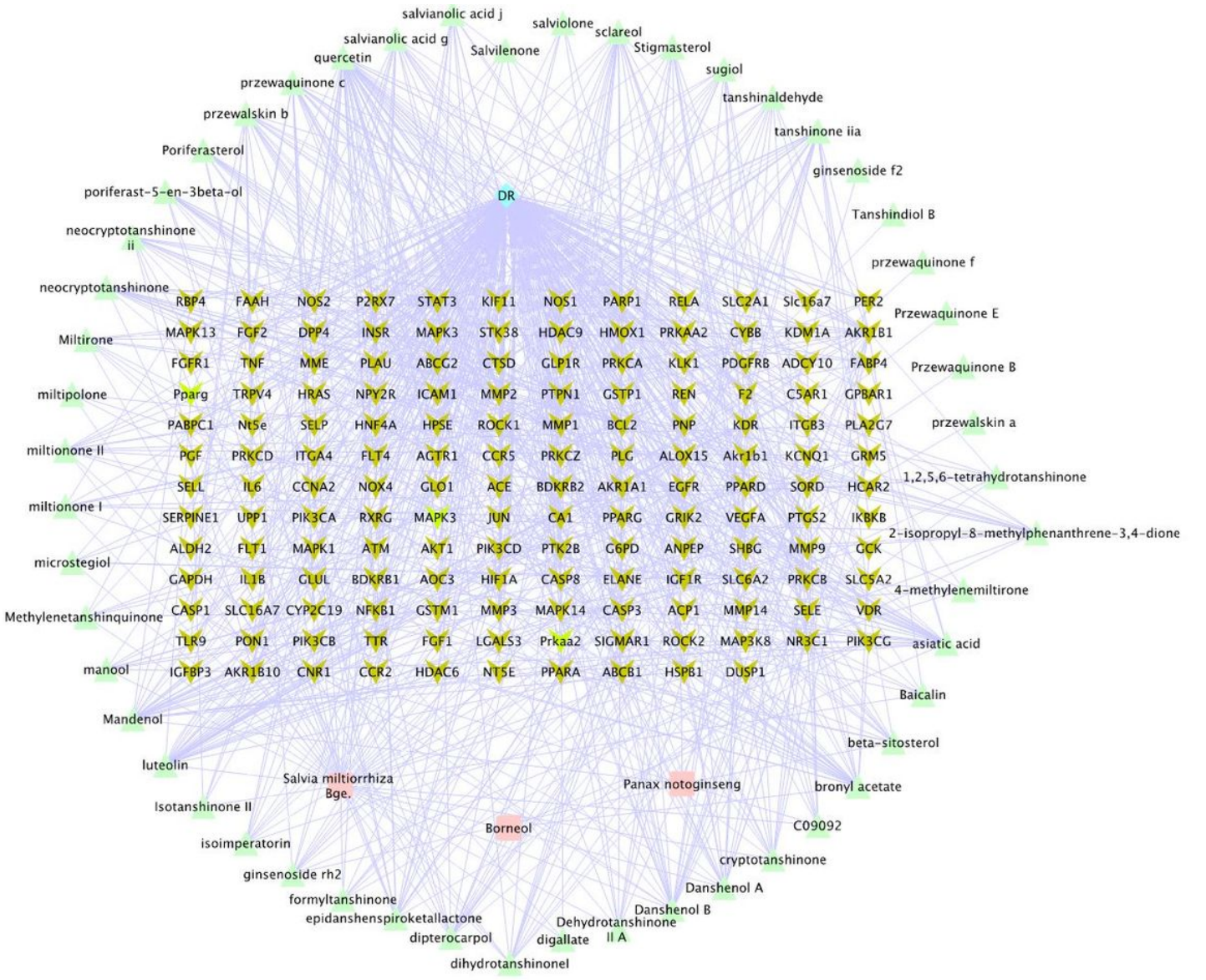

Figure 2

Drug-Component-Targets-DR network

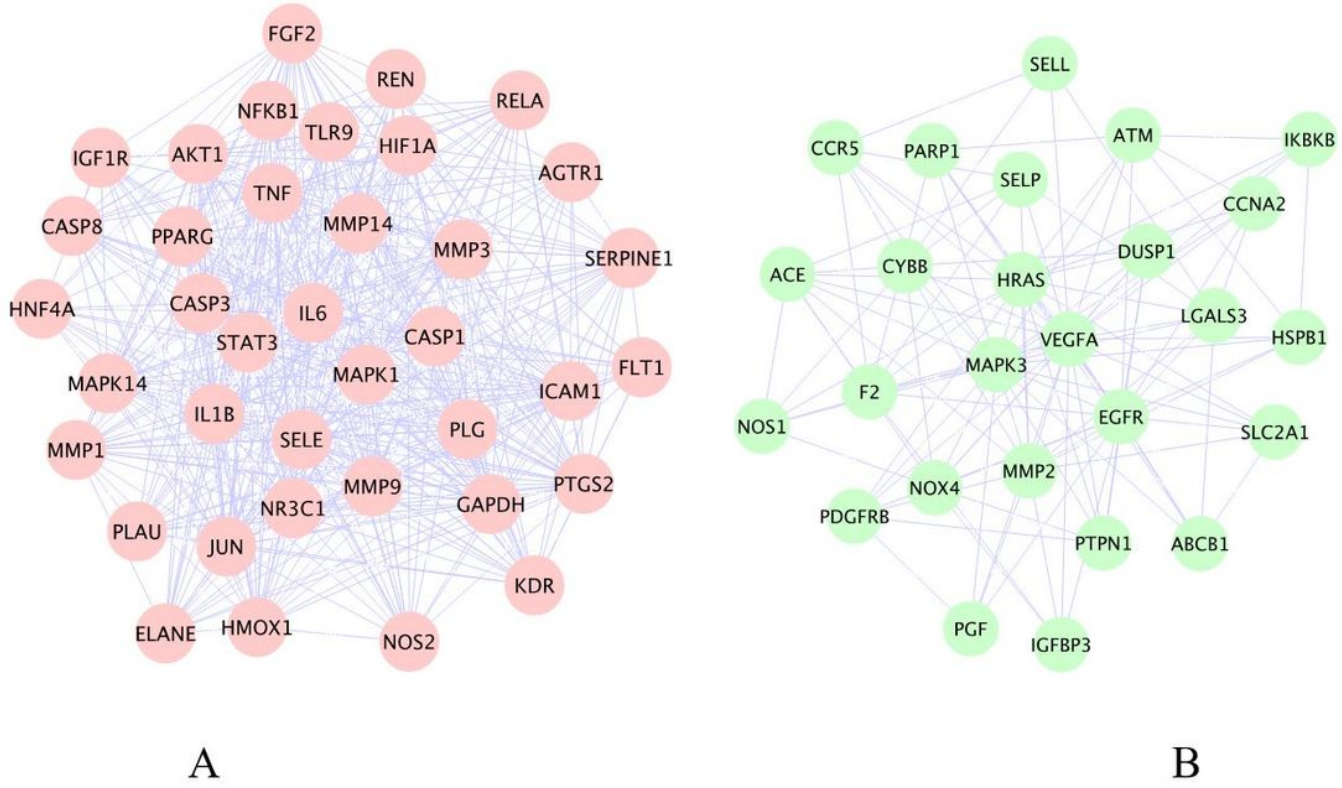

Figure 3

Clustering results of common targets

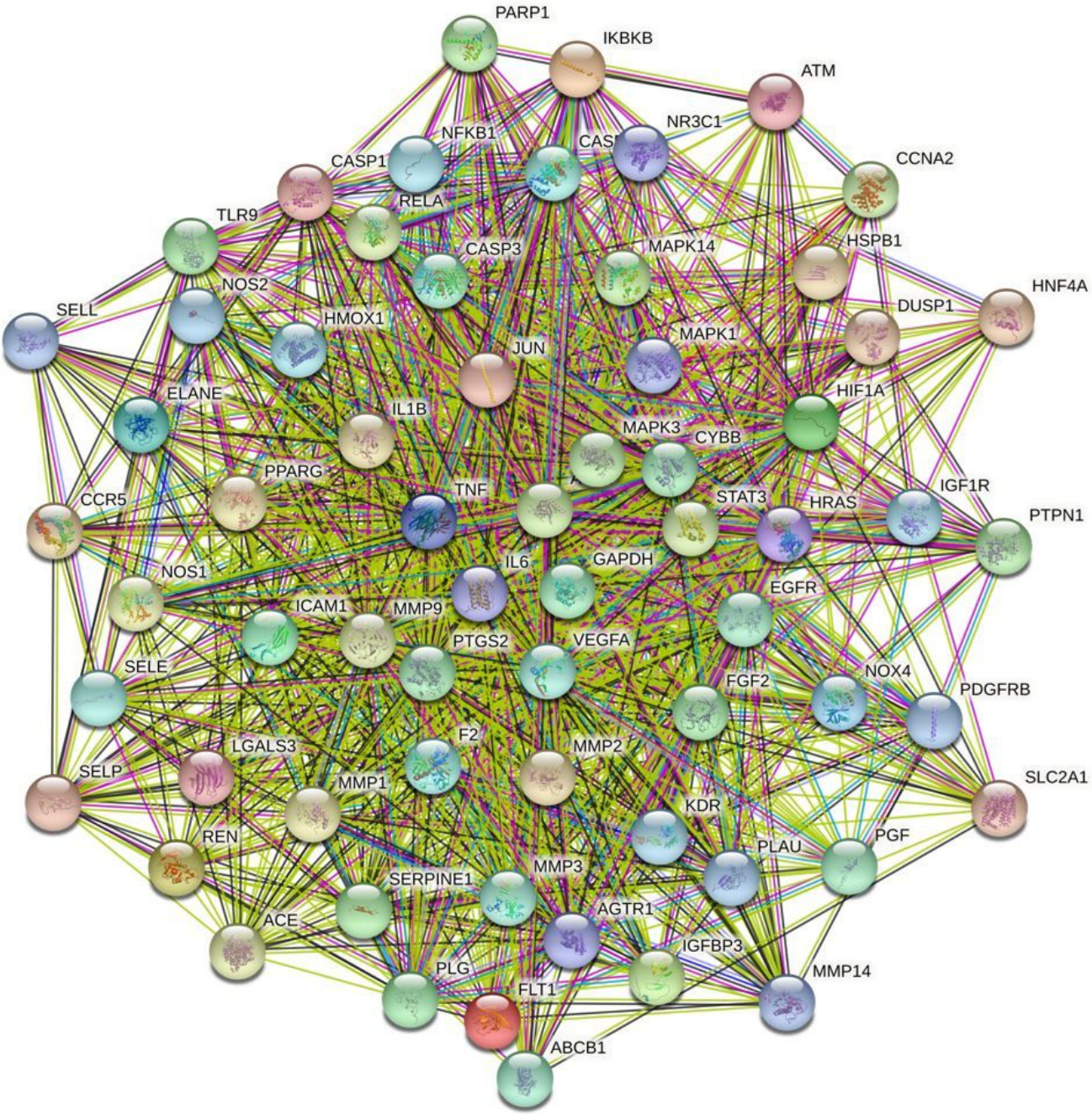

Figure 4

PPI results of co-targets

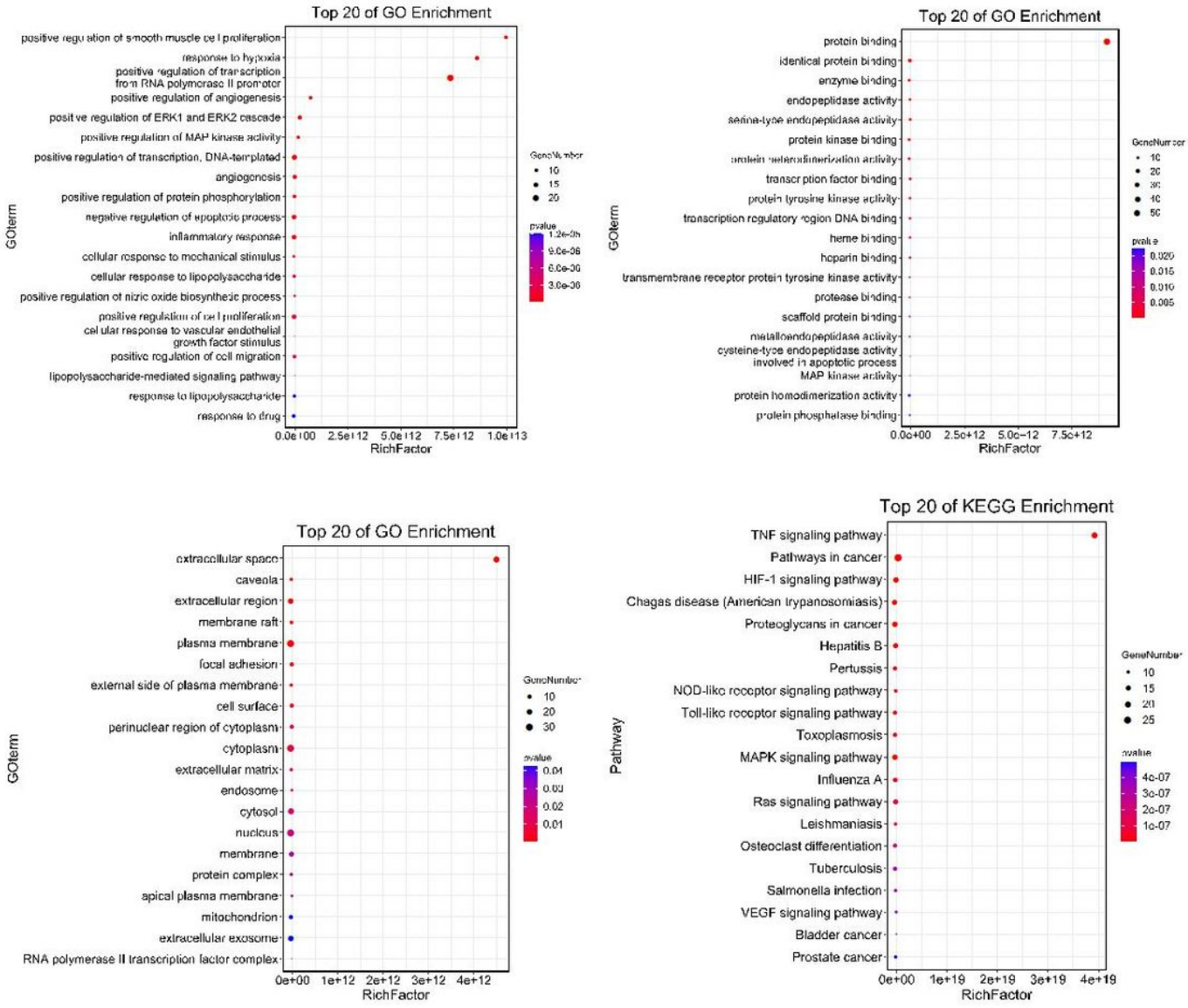

Figure 5

GO and KEGG signal pathway enrichment analysis

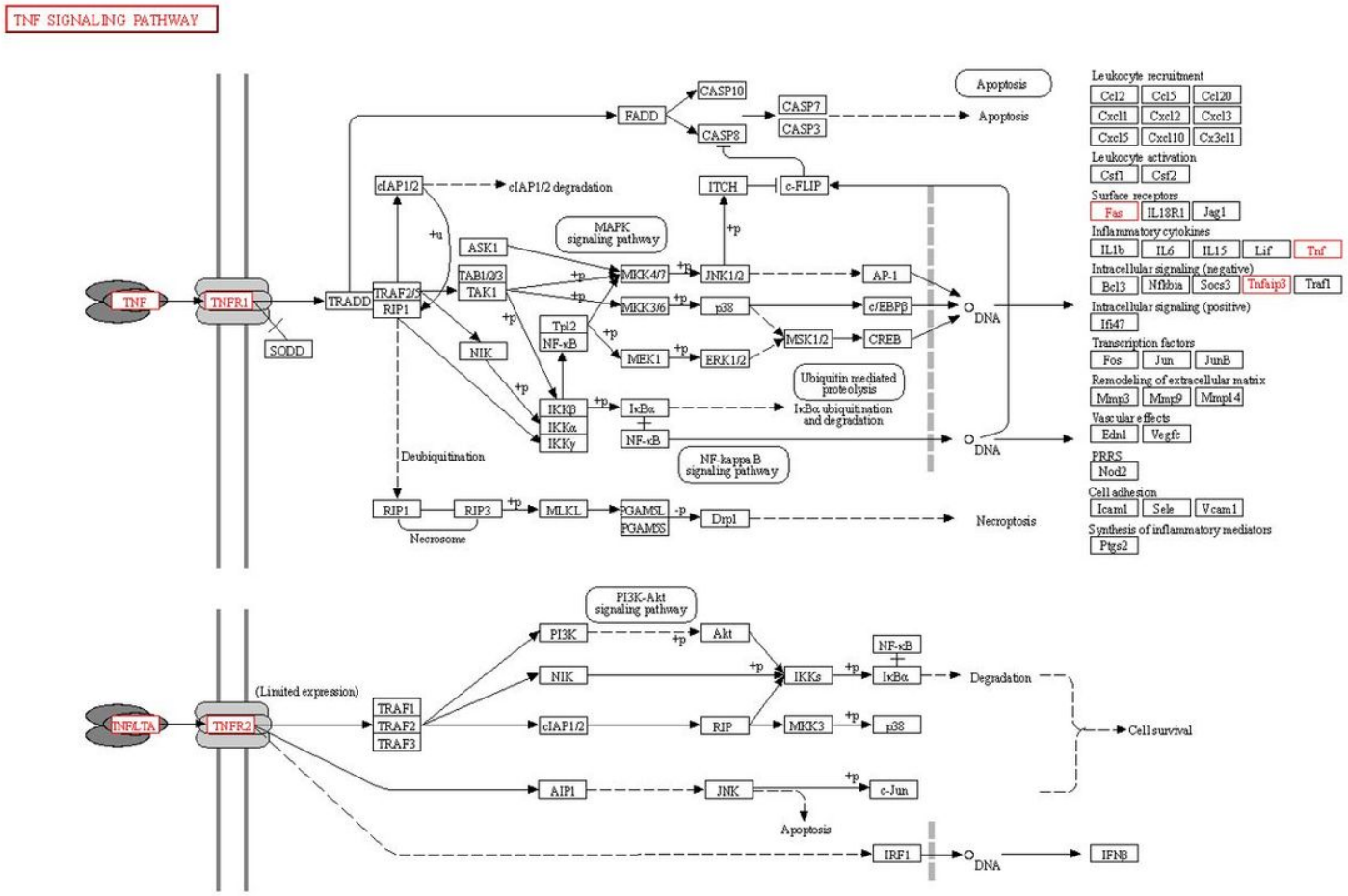

Figure 6

TNF signaling pathway

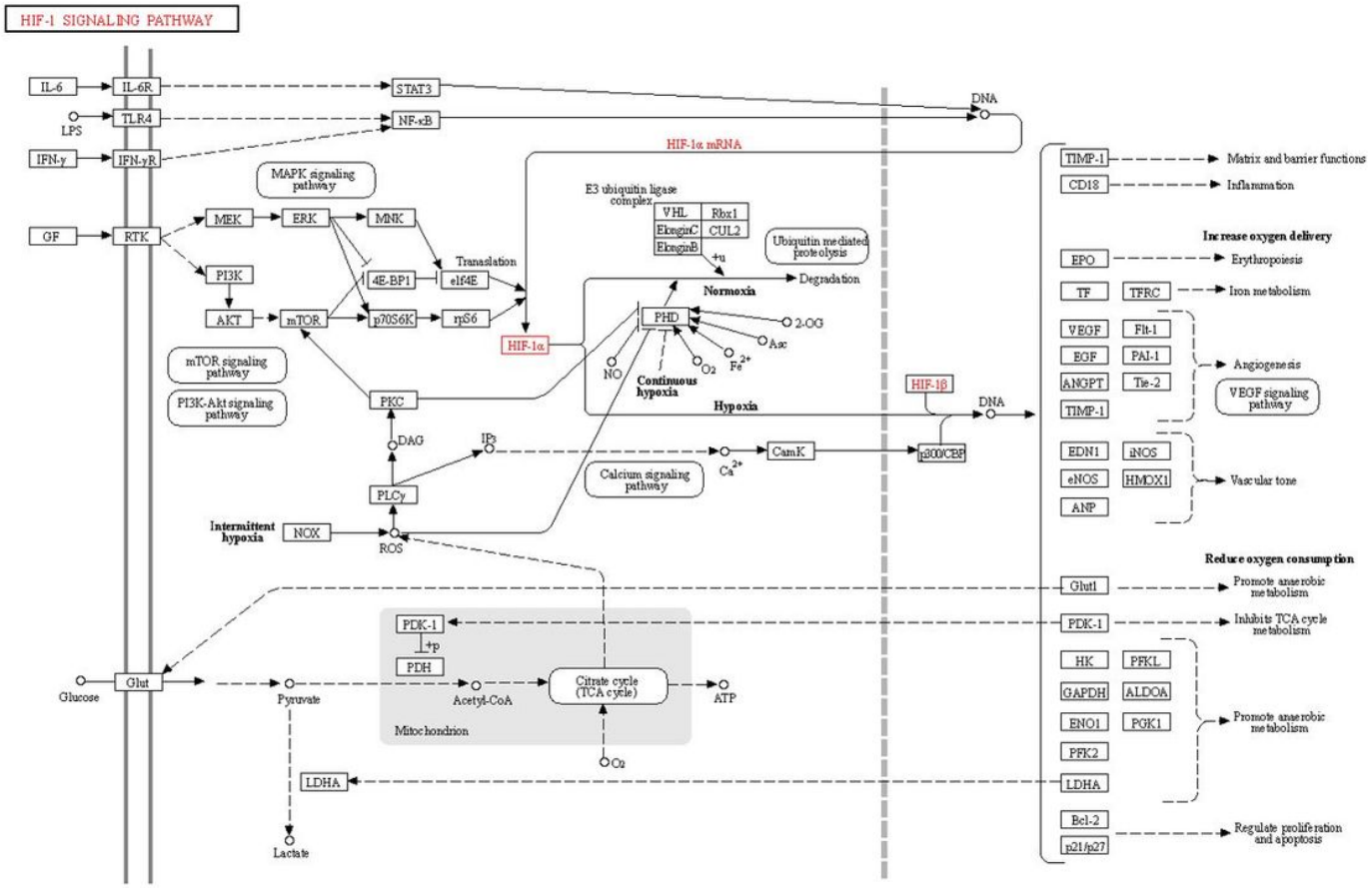

Figure 7

HIF-1 signaling pathway

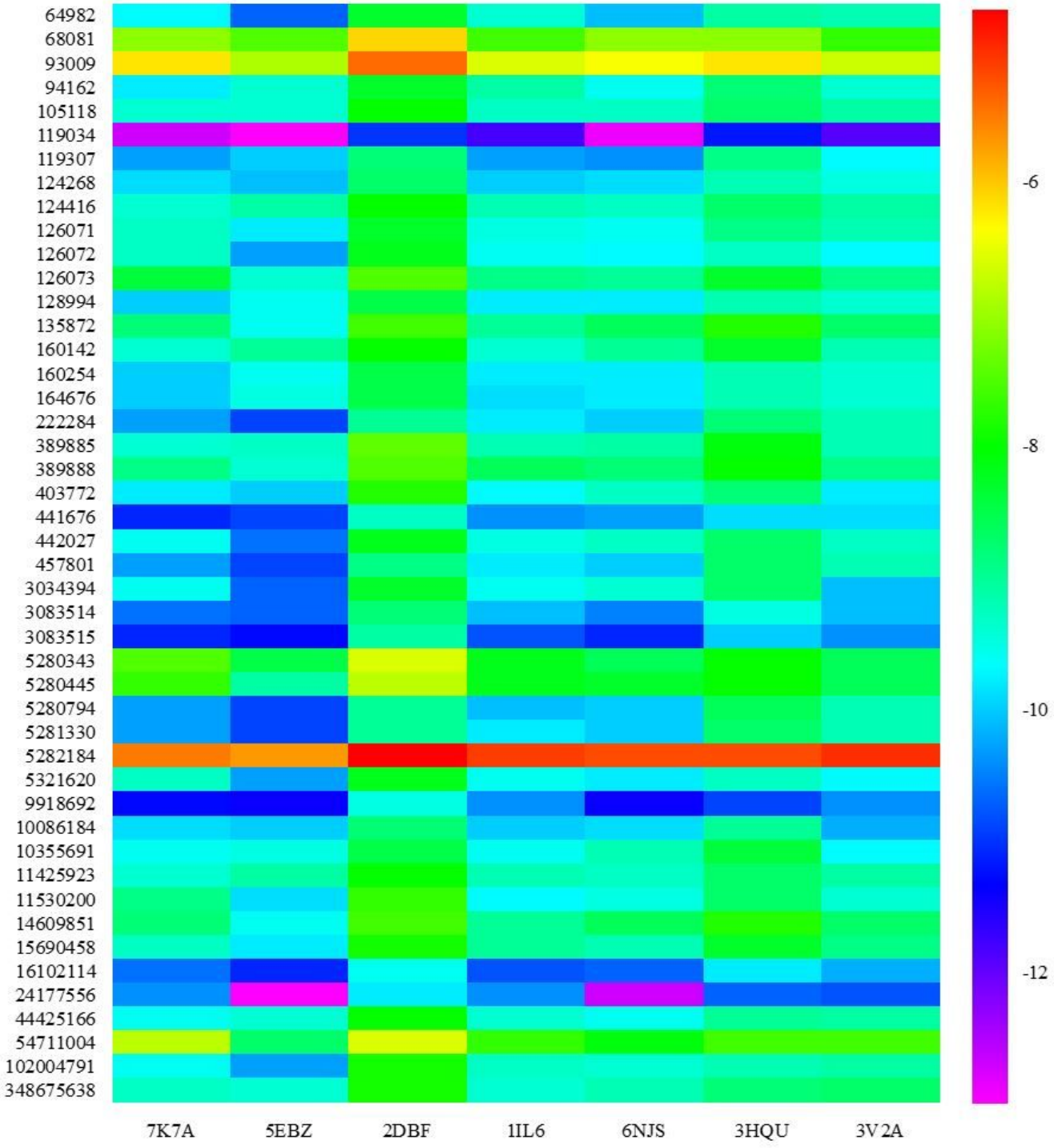

Figure 8

Molecular docking thermogram of 46 compounds in CDDP with TNF and HIF-1 signaling pathway

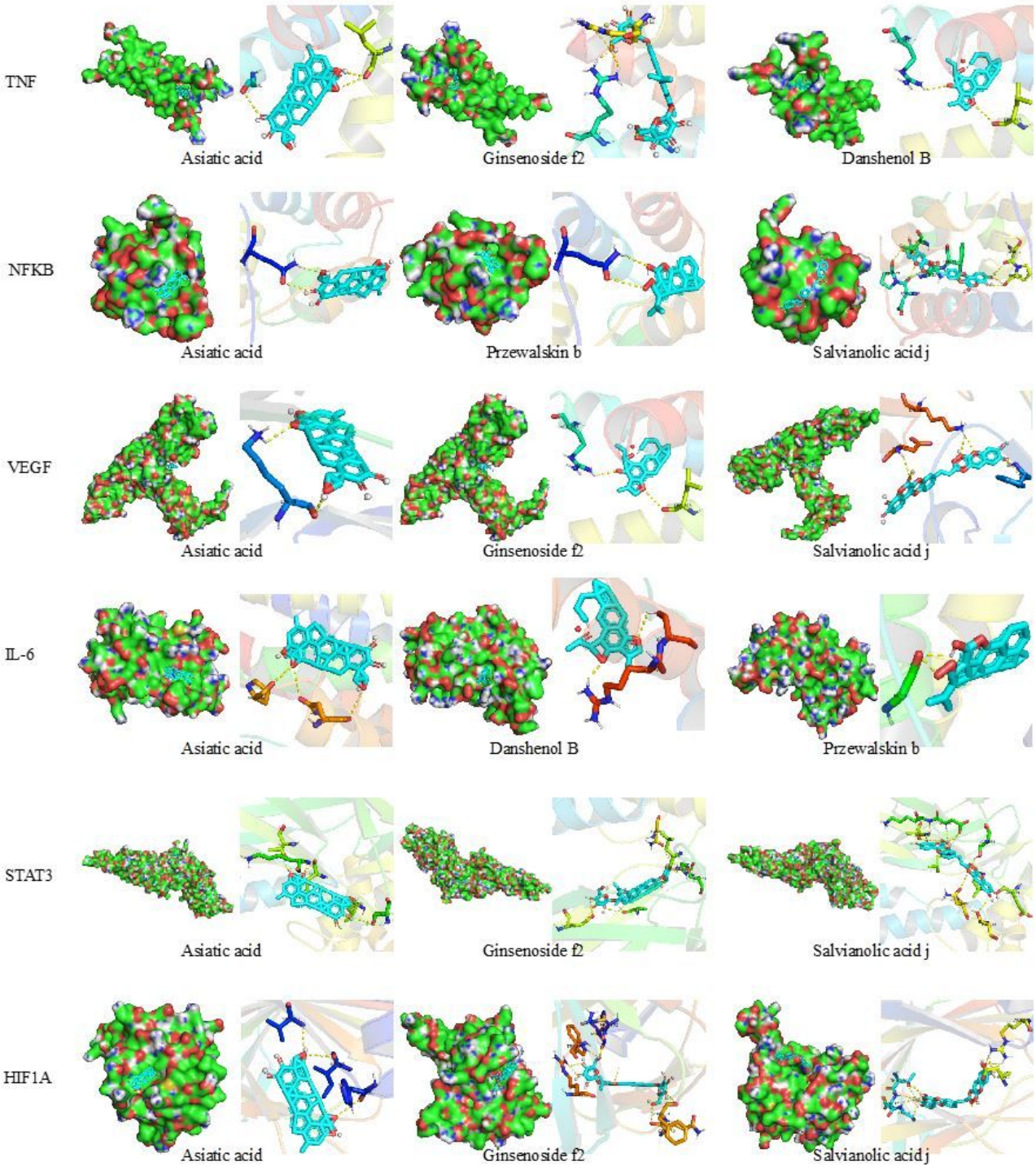

Figure 9

Visualization of docking results