



Investigating the molecular mechanism of Compound Danshen Dropping Pills for the treatment of epilepsy by utilizing network pharmacology and molecular docking technology

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Background: Compound Danshen Dropping Pills (CDDP) is widely used in clinical treatment of epilepsy. But the underlying active ingredients and molecular mechanisms are unclear. Our study aims to investigate the active components and functional mechanisms of CDDP in treating epilepsy using a network pharmacology approach.

Methods: Candidate constituents and targets of CDDP were searched on the Traditional Chinese Medicine Systems Pharmacology database. NCBI and Genecards were used to establish a database of epilepsy targets. Next, used Cytoscape software, the interactive network diagram of “drug-active component-target” was drawn. Based on the STRING database we constructed protein-protein interaction network and analyzed protein-protein interaction relationships. Gene ontology analysis and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis were performed for the common targets. Molecular docking provided an evaluation tool for verifying the combination of components and targets, which was performed using Auto-dock.

Results: Sixty bioactive components, corresponding to 79 therapeutic targets for epilepsy, were successfully identified. Functional enrichment analysis showed that CDDP plays a pharmacological role in the treatment of epilepsy by regulating serotonergic synapses, morphine addiction, nicotine addiction and other pathways, as well as the *NF-κB* signaling pathway. Molecular docking analysis showed that representative components may be closely bound to key targets.

Conclusions: This network pharmacology study revealed the synergistic effects of multiple components, targets, and pathways of CDDP in the treatment of epilepsy, which will deepen our understanding of the underlying molecular mechanisms of CDDP in the treatment of epilepsy and lay the foundation for further experimental studies.

Keywords: Compound Danshen Dropping Pills (CDDP); epilepsy; molecular docking; network pharmacology

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Introduction

Epilepsy is characterized by spontaneous convulsive behavior and abnormal brain discharge, and it is a very common chronic nervous system disease. Its incidence range is broad, and approximately 0.5–1% of people suffer from epilepsy worldwide (1). There are about 70 million epilepsy patients in the world (2).

The pathogenesis of epilepsy is complex, including abnormal excitation of the central nervous system, abnormal discharge of ion channels, genetic factors, and immune system diseases (3). It is considered that the enhancement of cortical excitability caused by the imbalance of brain excitation and inhibition mechanism are vital for pathophysiological of epilepsy (4). Epidemiological investigation has shown that the prevalence of epilepsy globally is close to 1 ‰, and the total number of epilepsy patients in the world has exceeded 50 million (5). Furthermore, epilepsy in the elderly may significantly increase the risk of fracture or abnormal fall injury (6–8). At the same time, epilepsy patients are more prone to sudden death of unknown cause (9). At present, the treatment of epilepsy is mainly pharmacological, which can effectively control seizures, but also increase the risk of suicide or other various concurrent diseases to a certain extent, such as exfoliative dermatitis, polycystic ovary syndrome, etc. (10–12). Therefore, epilepsy has become one of the major diseases endangering human health.

At present, antiepileptic drugs such as sodium valproate, carbamazepine, and levetiracetam are mainly used to treat the disease. However, there are disadvantages including poor curative effect, easy tolerance, as well as significant toxicity and side effects. Traditional Chinese medicine can make up for these defects and play an important role in the treatment of epilepsy; it has good curative effect, with long-lasting efficacy and few side effects. Compound Danshen Dropping Pills (CDDP) can reduce inflammatory reactions, control seizures, improve learning and memory function, and repair hippocampal neuron damage. The main components of CDDP are borneol, *Salvia miltiorrhiza* and *Panax notoginseng*. It is a traditional Chinese medicine dropping pill developed based on compound Danshen tablets under the guidance of traditional Chinese medicine theory. It has a wide range of clinical applications, such as the treatment of coronary heart disease, acute myocardial infarction and other diseases. In addition, it is widely used in clinical treatment of epilepsy, but its pharmacological mechanism is still unclear (3).

Network pharmacology emphasizes the strategy shift from “one target, one drug” strategy to the new method of “network target, multi-component” (13–16). CDDP and other traditional Chinese medicines have the potential to promote the development of multi-component and multi-target synergistic therapy for epilepsy.

With network pharmacology, we investigated the underlying anti-epileptic mechanism of CDDP. Firstly, we obtained the potential target genes of CDDP, and then studied the pathways shared by CDDP and the molecular targets of epilepsy. We conducted molecule docking to investigate the interaction between important compounds and targets. Compared with previous studies, we calculated the Root Mean Square Deviation (RMSD) value of docking to ensure the accuracy of docking results. Our results may help to clarify how CDDP can effectively treat epilepsy and promote the developing new drugs.

We present the following article in accordance with the STREGA reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-195/rc>).

Methods

Target genes related to epilepsy

Epilepsy-related genes were searched through the National Center for Biotechnology Information (<https://www.ncbi.nlm.nih.gov/>) (17) and Genecards (<https://www.genecards.org/>) (18) databases using “epilepsy” and “Homo sapiens” as the search terms. The targets of both databases were synthesized to delete duplicate values and obtain the relevant epilepsy targets. Seven hundred and twenty-nine targets were obtained from the NCBI, and 2,088 targets were retrieved with Genecards (score ≥ 1). After excluding the duplicated targets, we obtained a total of 2,234 targets. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Prediction of protein-encoding genes that are targeted by CDDP

The Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) is a frequently used database to study mechanisms of Traditional Chinese medicines (19). We searched the TCMSP for the components of CDDP, including *Salvia miltiorrhiza* Bge., *Panax notoginseng* (Burk.) F. H. Chen, Borneol. Each component was obtained by using oral bioavailability

(OB) $\geq 30\%$ and drug likeness (DL) ≥ 0.18 as the screening parameters (20).

Potential target genes of CDDP treating epilepsy

Shared target genes between epilepsy and the CDDP-related genes were intersected using a Venn diagram. We considered shared genes to be potential target genes of CDDP treating epilepsy.

The “drug-active component-target” network construction

CDDP active components and common genes were imported into the cytoscape 3.8.1. to build a “drug-active ingredient-target” network.

Construction of the target gene network

With STRING database (<http://string-db.org/cgi/input.pl>) and defining the species as “Homo sapiens” (21), a protein-protein interaction (PPI) network of intersecting genes of CDDP acting on epilepsy was constructed. The PPI data was downloaded and saved in TSV format. In addition, Cytoscape software (Institute of Systems Biology, the US) and its network analyzer tools were used to determine the accuracy of each target gene when selecting the core target.

Cluster analysis

Using Molecular Complex Detection (MCODE), the most important modules of PPI network were identified (22).

Analysis of gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment

Cytoscape clue GO was used for GO analysis, KEGG analysis of final target. The GO and KEGG pathway analyses were set as $P < 0.05$.

Molecular docking

Molecular docking was intended to validate interactions between the central targets and major active ingredients. We downloaded the protein crystal structure by searching the Research of Cooperative Organization for structural bioinformatics (RCSB) protein database (<http://www.pdb.org/>). The conformation of the protein was modified using Pymol (Schrödinger, the US) and Autodock1.5.6 (Olson

Laboratory of Scripps Institute, the US) software, including the removal of ligand and water, the addition of hydrogen, the optimization of amino acids, and the calculation of charge. Structural files of the key components are then downloaded through TCMSP, and with Chem3D software (Cambridgesoft, the US), their energy is minimized. The natural format of components and proteins was converted to the PDBQT format. Using AutoDock Vina, we performed molecular docking, and Discovery Studio 2019 (Beijing Chuangteng Technology Co., Ltd., China) was used to visualize docking results.

Results

Main components of CDDP

We obtained 336 chemical components of CDDP through TCMSP, including 76 components with OB $\geq 30\%$ and DL ≥ 0.18 . 65 components were included in Radix Salviae (Danshen), three components were included Borneolum Syntheticum (Bingpian), and eight compounds were included Panax Notoginseng (Burk.) F. H. Chen Ex C. Chow (Sanqi). After eliminating compounds without targets, 60 compounds remained. *Table 1* and *Figure 1A* had shown the active components and their OB and DL values.

The targets of CDDP in the treatment of epilepsy

Through TCMSP database, we searched 197 CDDP targets. According to the NCBI and Genecards database, 2,234 epilepsy targets were obtained. Finally, 79 CDDP targets were identified in epilepsy treatment (*Figure 1B*).

‘Drug-active component-target’ network analysis

We used cytoscape software to construct “drug-ingredient-target” networks. A total of 336 CDDP components were identified from the TCMSP. In this study, 76 bioactive components were screened, 16 of which had no target. Through TCMSP database, 60 components were obtained. The red nodes represented the drugs of CDDP, and the green nodes represented the CDDP active ingredients. Blue nodes represented potential CDDP targets, and the edges indicate the association between ingredients and targets (as shown in *Figure 2*).

PPI network analysis

Using Cytoscape 3.8.1 and based on 79 candidate targets,

Table 1 Basic information of CDDP components

Mol ID	Molecule name	MW	OB (%)	DL	Source
MOL001659	Poriferasterol	412.77	43.82985	0.75596	Radix Salviae
MOL007063	Przewalskin a	398.49	37.1065	0.64901	Radix Salviae
MOL007141	Salvianolic acid g	340.3	45.56486	0.60602	Radix Salviae
MOL007081	Danshenol B	354.48	57.95088	0.55764	Radix Salviae
MOL007093	Dan-shexinkum d	336.41	38.88302	0.55453	Radix Salviae
MOL007082	Danshenol A	336.41	56.96525	0.52172	Radix Salviae
MOL007071	Przewaquinone f	312.34	40.30788	0.45925	Radix Salviae
MOL007150	(6S)-6-hydroxy-1-methyl-6-methylol-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-quinone	312.34	75.38588	0.4551	Radix Salviae
MOL007151	Tanshindiol B	312.34	42.66581	0.45303	Radix Salviae
MOL007152	Przewaquinone E	312.34	42.85485	0.45301	Radix Salviae
MOL007070	(6S,7R)-6,7-dihydroxy-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione	312.34	41.31046	0.453	Radix Salviae
MOL007079	Tanshinaldehyde	308.35	52.4747	0.45196	Radix Salviae
MOL007155	(6S)-6-(hydroxymethyl)-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione	310.37	65.25894	0.44871	Radix Salviae
MOL007045	3 α -hydroxytanshinone IIa	310.37	44.92934	0.44272	Radix Salviae
MOL007064	Przewalskin b	330.46	110.324	0.43809	Radix Salviae
MOL007120	Miltionone II	312.39	71.0297	0.43711	Radix Salviae
MOL007058	Formyltanshinone	290.28	73.44462	0.41736	Radix Salviae
MOL007059	3-beta-Hydroxymethylenetanshinquinone	294.32	32.16103	0.40894	Radix Salviae
MOL007069	Przewaquinone c	296.34	55.74167	0.40408	Radix Salviae
MOL002651	Dehydrotanshinone II A	292.35	43.76229	0.40019	Radix Salviae
MOL007154	Tanshinone IIa	294.37	49.8873	0.39781	Radix Salviae
MOL007111	Isotanshinone II	294.37	49.91603	0.39674	Radix Salviae
MOL007050	2-(4-hydroxy-3-methoxyphenyl)-5-(3-hydroxypropyl)-7-methoxy-3-benzofurancarboxaldehyde	356.4	62.78415	0.39628	Radix Salviae
MOL007088	Cryptotanshinone	296.39	52.34196	0.39555	Radix Salviae
MOL007108	Isocryptotanshinone	296.39	54.98193	0.39449	Radix Salviae
MOL007085	Salvilenone	292.4	30.38365	0.37639	Radix Salviae
MOL007121	Miltipolone	300.43	36.55611	0.36803	Radix Salviae
MOL007127	1-methyl-8,9-dihydro-7H-naphtho[5,6-g]benzofuran-6,10,11-trione	280.29	34.72082	0.36634	Radix Salviae
MOL007061	Methylenetanshinquinone	278.32	37.07319	0.36017	Radix Salviae
MOL007101	Dihydrotanshinone I	278.32	45.04328	0.36015	Radix Salviae
MOL001601	1,2,5,6-tetrahydrotanshinone	280.34	38.74539	0.35791	Radix Salviae
MOL007132	(2R)-3-(3,4-dihydroxyphenyl)-2-[(Z)-3-(3,4-dihydroxyphenyl)acryloyl]oxy-propionic acid	360.34	109.3805	0.35119	Radix Salviae

Table 1 (continued)

Table 1 (continued)

Mol ID	Molecule name	MW	OB (%)	DL	Source
MOL007125	Neocryptotanshinone	314.41	52.488	0.32306	Radix Salviae
MOL007100	Dihydrotanshinlactone	266.31	38.68477	0.32227	Radix Salviae
MOL007119	Miltionone I	312.39	49.68439	0.32125	Radix Salviae
MOL007048	(E)-3-[2-(3,4-dihydroxyphenyl)-7-hydroxy-benzofuran-4-yl]acrylic acid	312.29	48.24363	0.31229	Radix Salviae
MOL007130	Prolithospermic acid	314.31	64.37096	0.31017	Radix Salviae
MOL007094	Dan shen spiroketal lactone	282.36	50.43128	0.3067	Radix Salviae
MOL007105	Epidanshen spiroketal lactone	284.38	68.27316	0.30549	Radix Salviae
MOL007156	Tanshinone VI	296.34	45.63731	0.29549	Radix Salviae
MOL007036	5,6-dihydroxy-7-isopropyl-1,1-dimethyl-2,3-dihydrophenanthren-4-one	298.41	33.76525	0.28585	Radix Salviae
MOL007098	Deoxyneocryptotanshinone	298.41	49.40035	0.28555	Radix Salviae
MOL002222	Sugiol	300.48	36.11353	0.27648	Radix Salviae
MOL000569	Digallate	322.24	61.84862	0.25635	Radix Salviae
MOL007122	Miltirone	282.41	38.75699	0.25418	Radix Salviae
MOL007107	C09092	286.5	36.06949	0.2474	Radix Salviae
MOL000006	Luteolin	286.25	36.16263	0.24552	Radix Salviae
MOL007145	Salviolone	268.38	31.72415	0.23568	Radix Salviae
MOL007124	Neocryptotanshinone ii	270.35	39.46299	0.23157	Radix Salviae
MOL007041	2-isopropyl-8-methylphenanthrene-3,4-dione	264.34	40.86015	0.22897	Radix Salviae
MOL007143	Salvilenone I	270.4	32.43471	0.22895	Radix Salviae
MOL007049	4-methylenemiltirone	266.36	34.34868	0.22726	Radix Salviae
MOL001942	Isoimperatorin	270.3	45.46425	0.22524	Radix Salviae
MOL007077	Sclareol	308.56	43.67068	0.2058	Radix Salviae
MOL000449	Stigmasterol	412.77	43.82985	0.75665	Panax Notoginseng (Burk.) F. H. Chen Ex C. Chow
MOL000358	Beta-sitosterol	414.79	36.91391	0.75123	Panax Notoginseng (Burk.) F. H. Chen Ex C. Chow
MOL005344	ginsenoside rh2	622.98	36.31951	0.55868	Panax Notoginseng (Burk.) F. H. Chen Ex C. Chow
MOL000098	Quercetin	302.25	46.43335	0.27525	Panax Notoginseng (Burk.) F. H. Chen Ex C. Chow
MOL001494	Mandenol	308.56	41.9962	0.19321	Panax Notoginseng (Burk.) F. H. Chen Ex C. Chow
MOL001792	DFV	256.27	32.76272	0.18316	Panax Notoginseng (Burk.) F. H. Chen Ex C. Chow

CDDP, Compound Danshen Dropping Pills; MW, molecular weight; OB, oral bioavailability; DL, drug likeness.

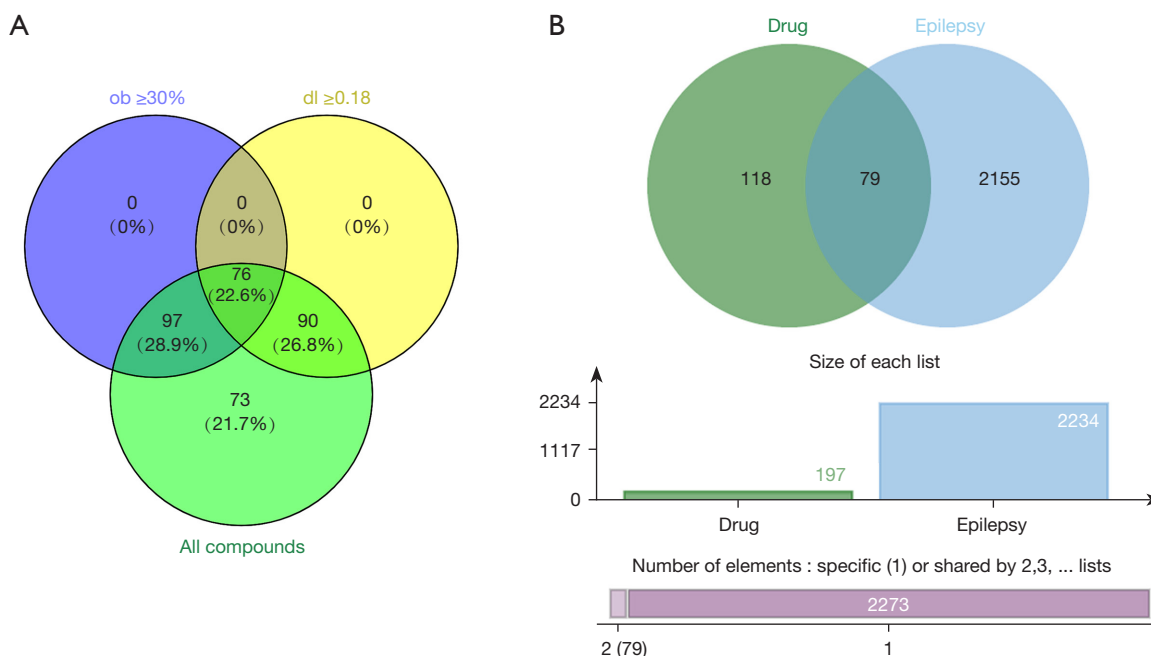


Figure 1 Compound Danshen Dropping Pills (CDDP) screening of bioactive compounds. (A) Venn diagram: based on absorption, distribution, metabolism, excretion (ADME)-related models, 76 bioactive components were screened [blue section stands for the components of oral bioavailability (OB) $\geq 30\%$, yellow section stands for drug likeness (DL) ≥ 0.18]; (B) Venn diagram of CDDP- and epilepsy-related targets; 79 common targets were obtained.

we established a PPI network. There were 79 nodes and 984 edges, where the average node degree was 24.9 and the local clustering coefficient was 0.698 (Figure 3). MCODE network analysis showed five clusters (Figure 4A-4E), and the scores were 31.737, 3.333, 3, 3, and 3 respectively. These proteins have important function in the PPI network, and the top five proteins were *AKT* serine/threonine kinase 1 (*AKT1*), cellular tumor antigen p53 (*TP53*), interleukin-6 (*IL-6*), tumor necrosis factor (*TNF*) (Figure 5A). The 11 compounds with the most targets are shown in Figure 5B.

Analysis of GO function and KEGG pathway enrichment

Through GO enrichment analysis, we obtained a total of 4,270 GO items, including 4,145 biological processes (BP) items, 11 cell components (CC) items, and 115 molecular functions (MF) items. The results showed that CDDP treatment of epilepsy BP was mainly related to the activation of adenylate cyclase activity, odontogenesis of dentin-containing tooth, including dentin, androgen metabolism, response to toxic substances, response to estrogen, and cellular response to estrogen stimulus. CC was mainly

involved in platelet alpha particles cavity, projection of cytoplasm, and dendrites neuronal cytoplasm, etc. MF was mainly involved in the activation of protein kinase B activity, tau protein kinase activity, protein kinase C binding, and adenylate cyclase activity, as shown in Figure 6A.

Based on KEGG pathway enrichment analysis, a total of 103 pathways were obtained. According to the P value, the top 20 items were shown in Figure 6B. These included the serotonergic synapse, morphine addiction, nicotine addiction, *NF- κ B*, and Nod-like receptor signaling pathways.

Molecular docking analysis

Quercetin, luteolin, and tanshinone IIa were selected as the key active ingredients to perform molecular docking with *AKT1*, *IL6*, and *TP53* (the basic information is shown in Table 2). The key active ingredients and hub targets were verified by molecular docking using the binding energy ≤ -5.0 kcal/mol as the standard (18). Docking results (shown in Figures 7-9 and Table 3) showed that the binding free energy of the key active ingredients of epilepsy and the hub target was far less than -5.0 kcal/mol, and the RMSD was

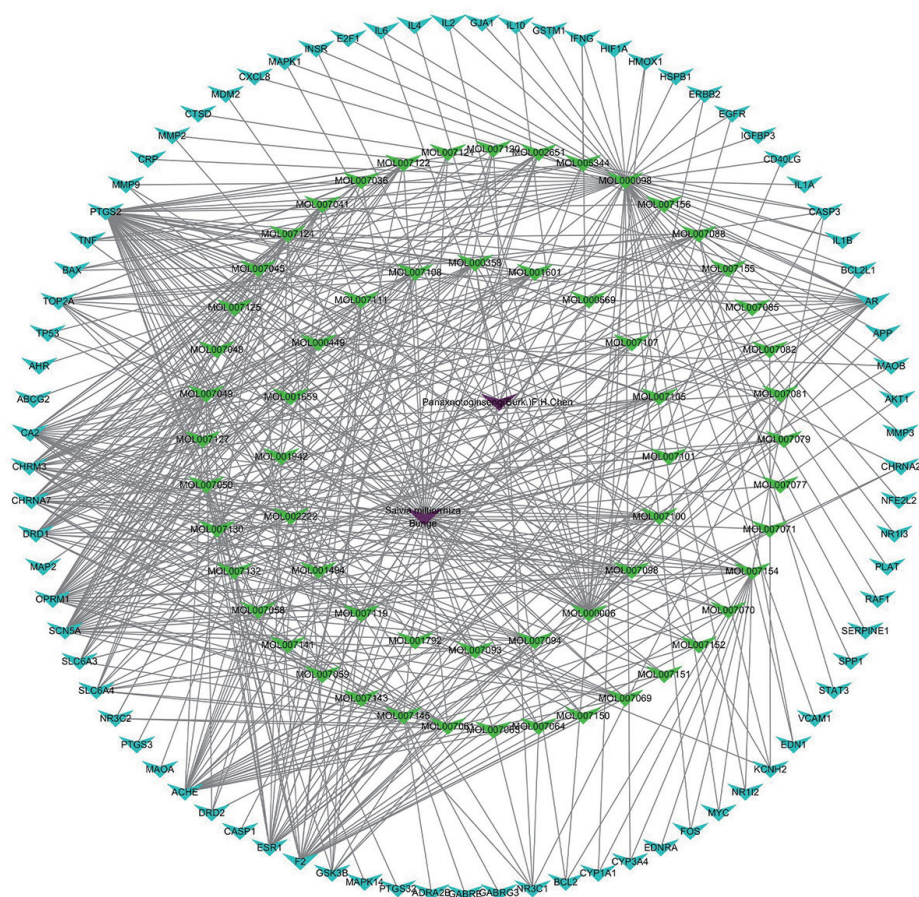


Figure 2 Mapping of Compound Danshen Dropping Pills (CDDP)- and epilepsy-related targets, 79 common targets were showed. Purple node denoted for drug, green nodes denoted for bioactive components, and blue nodes denoted for predicted targets.

less than 2, indicating that the important active ingredients of CDDP combined well with the hub targets. This indicates that the results of this study are reliable, as shown in *Figure 10*.

Discussion

Epilepsy is a very common neurological disease, characterized by recurrent epileptic seizures or abnormal behavior, feeling, and even loss of consciousness caused by the abnormal discharge of brain neurons (23). The annual incidence rate of active epilepsy in China is about 3.79 per thousand (24). The prevalence is the highest in 1-year old, and gradually decreases with age. Relevant studies (25,26) have shown that about a quarter of epilepsy cases can be prevented. In patients with epilepsy, about 60–70% of patients can achieve zero seizure through antiepileptic

drugs, but the long-term use of antiepileptic drugs may result in some side effects. In addition, a considerable number of epileptic patients are still unable to control seizures through drugs or surgery (27). Based on the above situation, the current research on epilepsy is mainly divided into two aspects: (I) the prevention and treatment of epilepsy, and (II) the health monitoring and nursing of patients with epilepsy. These studies involve multiple fields, including biology, medicine, rehabilitation, electronics, and computer science.

In recent years, research into the mechanism of traditional Chinese medicine epilepsy treatment has increased. Numerous studies have shown that traditional Chinese medicine can inhibit the occurrence and development of epilepsy by inhibiting apoptosis, regulating oxidative stress, and inhibiting inflammatory reactions (28,29). Epilepsy has the characteristics of long course

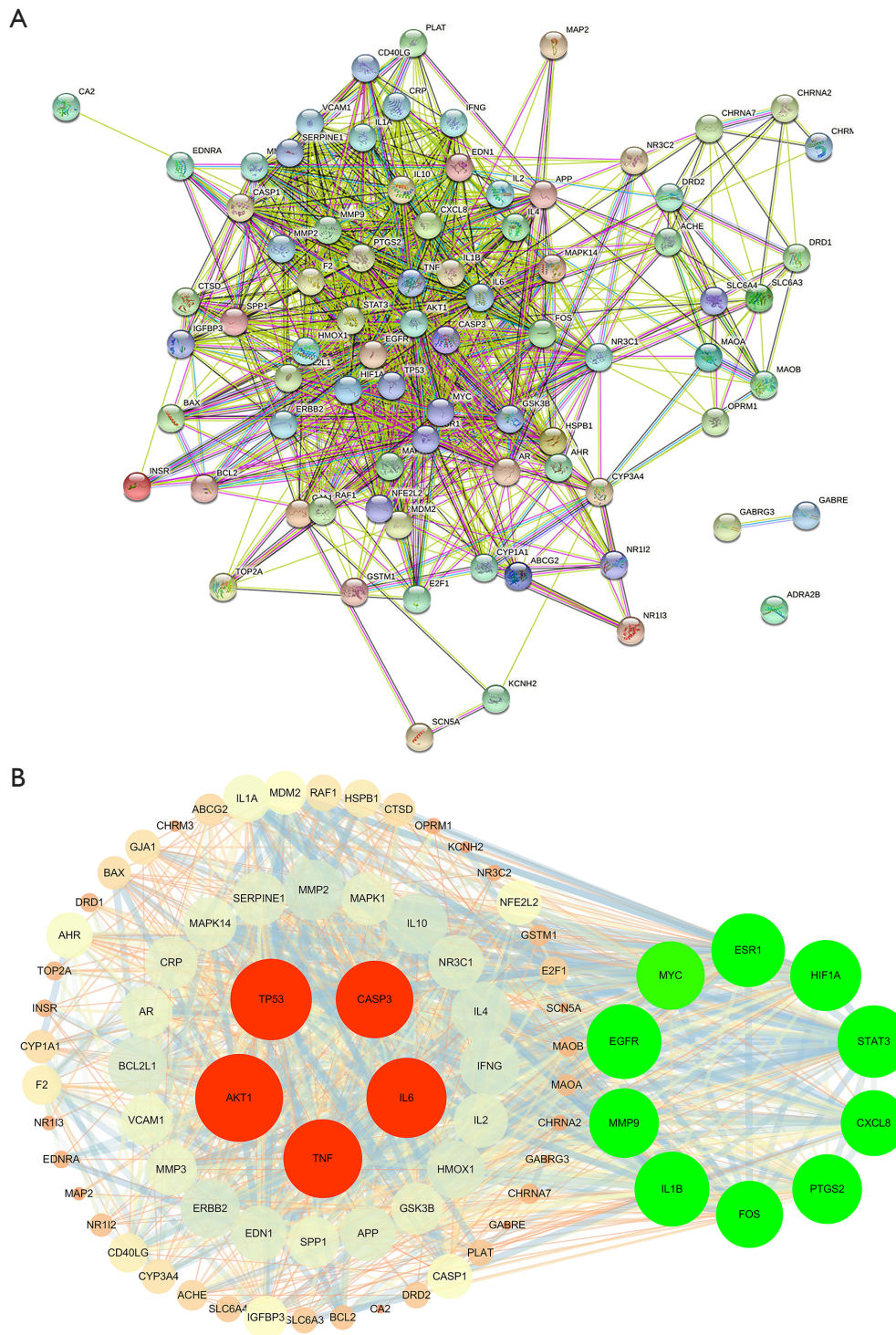


Figure 3 Common-target network. (A) Protein-protein interaction mapping by string database; (B) interaction network of Compound Danshen Dropping Pills (CDDP)-related targets. The red nodes represented the key targets.

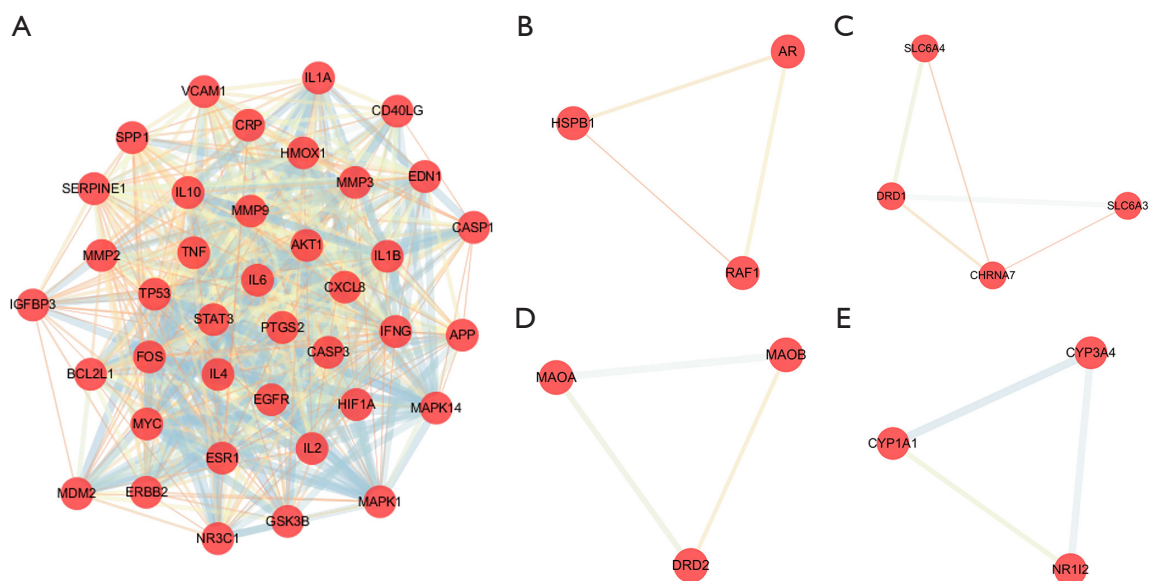


Figure 4 Subnetwork graph of protein-protein interaction. (A) Score =31.737; (B) Score =3.33; (C) Score =3; (D) Score =3; (E) Score =3.

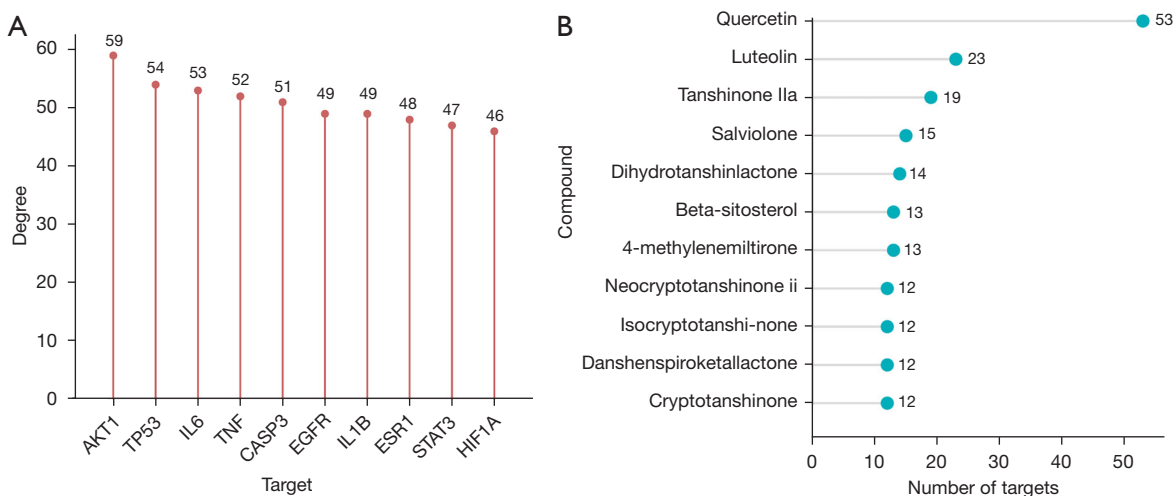


Figure 5 Hub targets and active ingredients. (A) Degree level of each hub-target; (B) number of targets corresponding to important active ingredients.

of disease, recurrent seizures, and curative difficulty. Traditional Chinese medicine has the characteristics of obvious curative effect, multi-target, multi-channel, as well as minimal toxicity and side effects in the prevention and treatment of epilepsy. Therefore, in-depth study of the signaling pathway mechanisms in epilepsy and the development of more effective antiepileptic drugs are the focus of future research.

Based on the method of network pharmacology, we

clarify the mechanism of CDDP in the treatment of epilepsy. Quercetin is one of the most abundant flavonoids in nature, and has antioxidant, anti-inflammatory, anti-tumor, and antiviral neuroprotective effects (30,31). Quercetin can reduce lipid peroxidation and increase endogenous antioxidant enzymes in the brain, so as to reduce the frequency and severity of seizures (32). It is reported that quercetin can resist apoptosis and protect neurons by increasing X-linked inhibitor of apoptosis protein

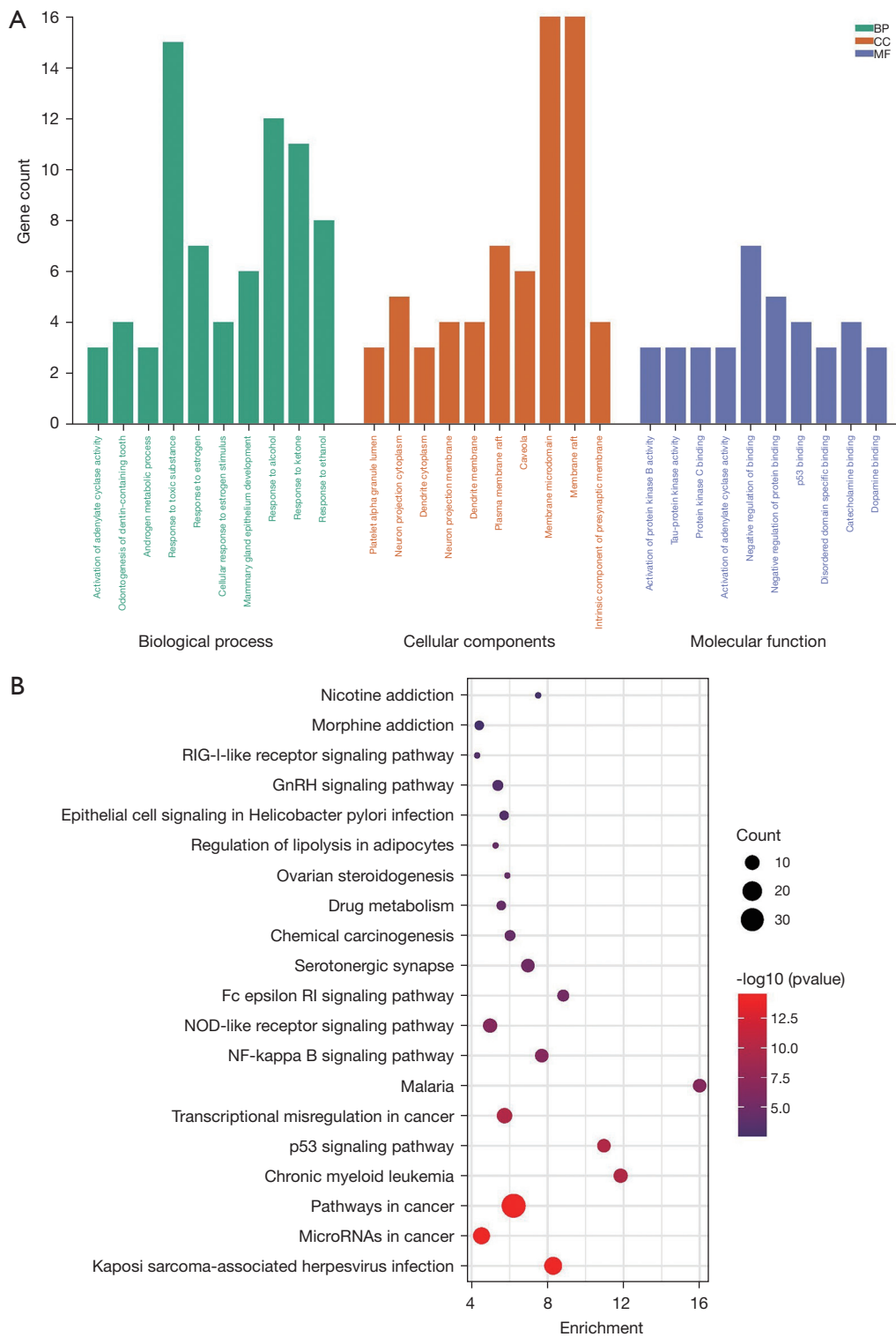


Figure 6 Enrichment of gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways of Compound Danshen Dropping Pills (CDDP) treating epilepsy. (A) Enriched gene ontology terms; (B) enriched KEGG pathways.

Table 2 Basic information of the key targets

GC ID	Symbol	Degree	Description
GC14M104769	AKT1	59	AKT serine/threonine kinase 1
GC17M007661	TP53	54	Tumor protein P53
GC07P022725	IL6	53	Interleukin 6

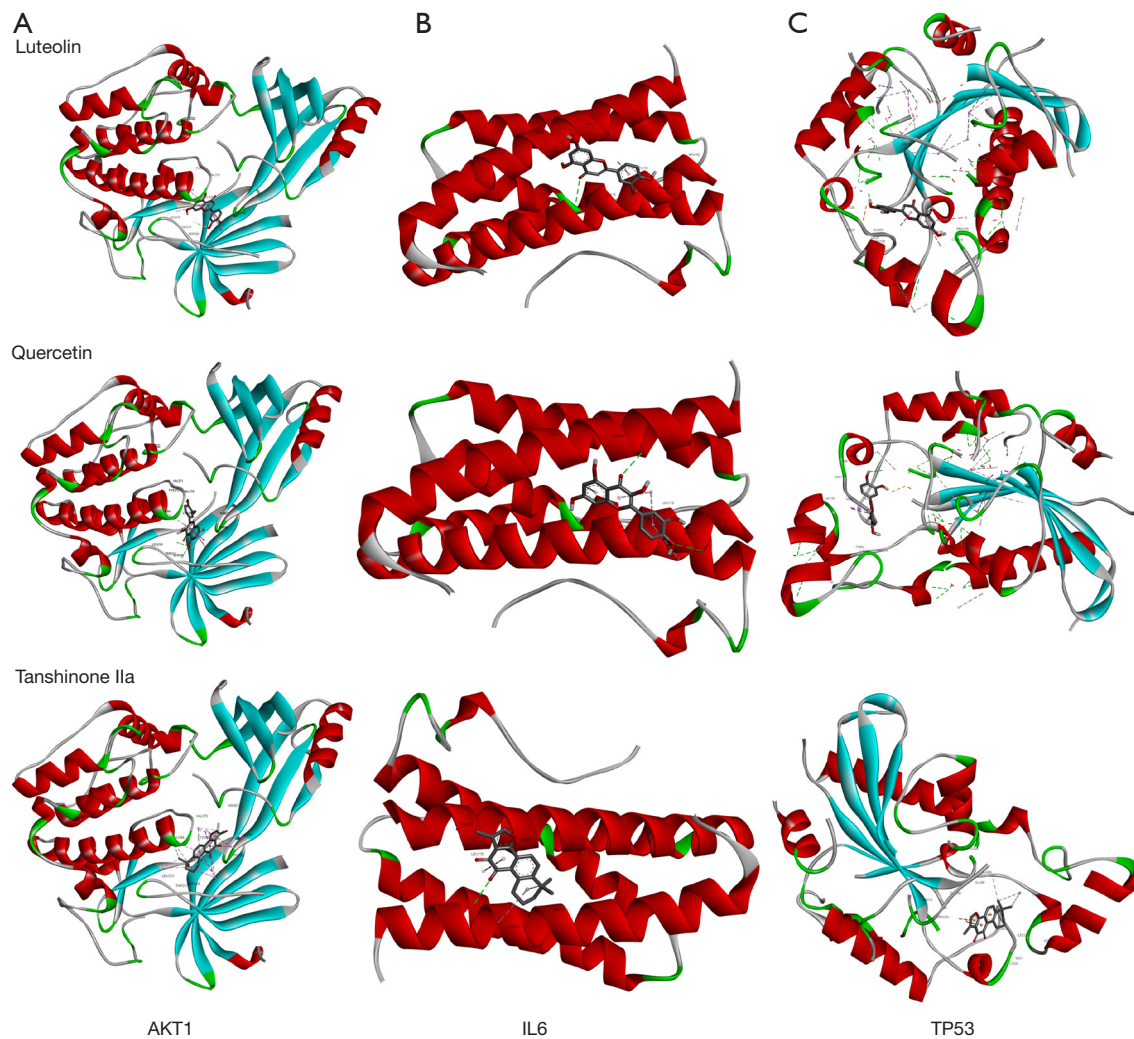


Figure 7 The three targets were as follows: interleukin-6 (*IL6*, PDB ID: 1alu), *AKT* serine/threonine kinase 1 (*AKT1*, PDB ID: 6s9x), and tumor protein p53 (*TP53*, PDB ID: 3dcy). The top three compounds were luteolin, quercetin, and tanshinone IIa. The binding energy ranged from -10.9 to -5.10 kcal/mol. Structural model of active ingredients with key targets. (A) Structural model of *AKT1* with luteolin, quercetin, and tanshinone IIa; (B) structural model of *IL6* with luteolin, quercetin, and tanshinone IIa; (C) structural model of *TP53* with luteolin, quercetin, and tanshinone IIa.

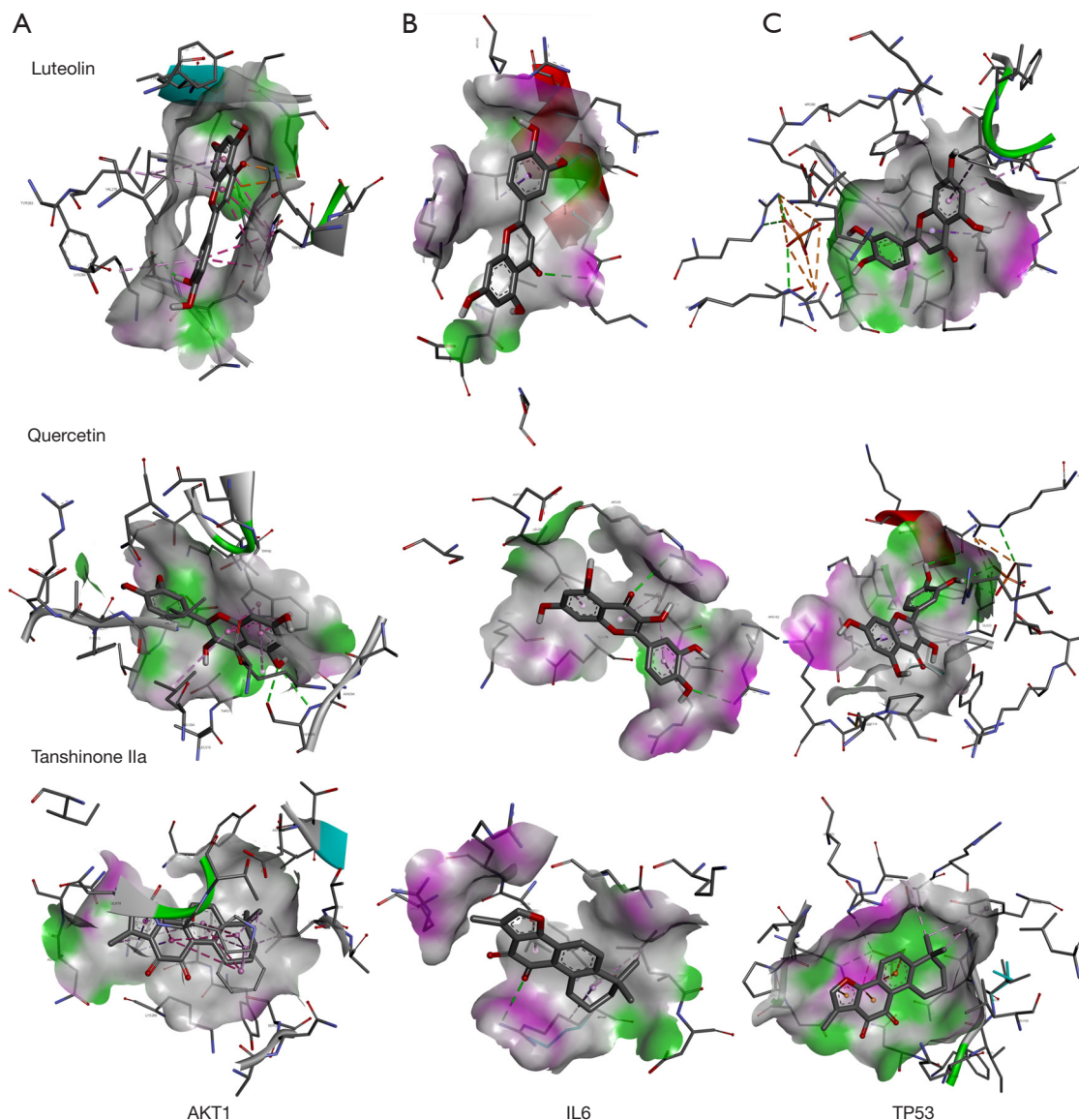


Figure 8 Binding mode of proteins and ligands. (A) binding mode of *AKT* serine/threonine kinase 1 (*AKT1*) with luteolin, quercetin, and tanshinone IIa; (B) binding mode of interleukin-6 (*IL6*) with luteolin, quercetin, and tanshinone IIa; (C) binding mode of tumor protein *p53* (*TP53*) with luteolin, quercetin, and tanshinone IIa.

(XIAP) expression and inhibiting caspase-3 activity in the hippocampus (33). Based on Morris water maze experiment, D’Hooge *et al.* found that the latency of looking for the platform was prolonged and the residence time in the hidden platform quadrant was shortened, indicating the decline in learning and memory ability (34). Tanshinone IIa is the main fat soluble component of *Salvia miltiorrhiza*, a diterpene quinone compound. It has pharmacological activities in cardiovascular diseases, anti-tumor, anti-inflammatory,

anticoagulant, and improving organ fibrosis (35). Using pentylenetetrazole induced juvenile zebrafish and mouse epilepsy models, it was found that tanshinone IIa may play an anticonvulsant role by activating the γ -aminobutyric acid (*GABA*) signaling pathway. Tanshinone IIa can also protect against lead-induced neurobehavioral defects in rats (36). In addition, our research group’s previous study found that tanshinone IIa may alleviate epileptic seizures in epileptic rats by regulating the brain-derived neurotrophic

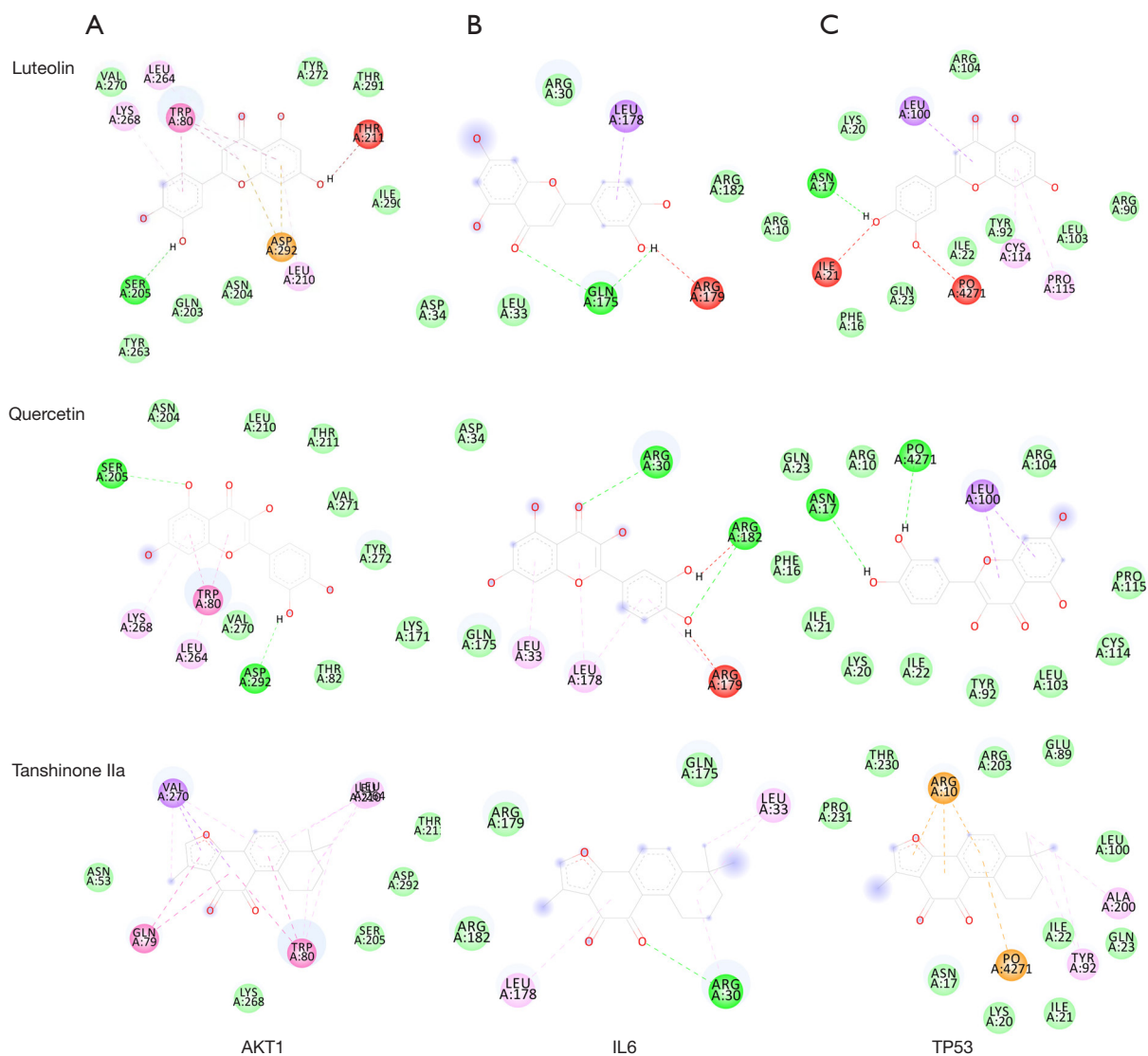


Figure 9 Binding site of key targets and active ingredients. (A) binding site of *AKT* serine/threonine kinase 1 (*AKT1*) with luteolin, quercetin, and tanshinone IIa; (B) binding site of interleukin-6 (*IL6*) with luteolin, quercetin, and tanshinone IIa; (C) binding site of tumor protein *p53* (*TP53*) with luteolin, quercetin, and tanshinone IIa.

factor- Tyrosine Kinase receptor B (*BDNF TrkB*) pathway, enhance the expression of hippocampal synaptic remodeling proteins, syn and *PSD-95*, in epileptic rats, regulate synaptic plasticity, and subsequently improve the cognitive function of epileptic rats.

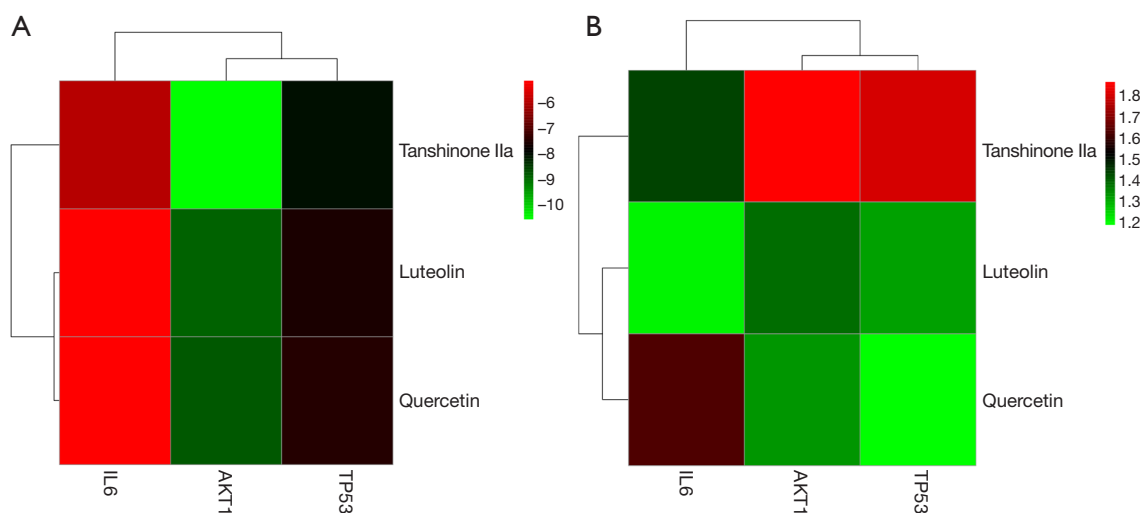
Interleukin 6 (*IL6*) is a commonly used inflammatory factor in the clinic, which can promote the proliferation and functional changes of glial cells and participate in the regulation of neuronal function. Studies have shown that *IL6* is a neuroprotective factor, which can protect nerve

cells, repair damaged neurons and reduce epileptic brain injury (37,38). *P38* is an important member of the mitogen-activated protein kinase (*MAPK*) family. It causes nuclear translocation after activation and leads to phosphorylation activation for many protein kinases and transcription factors, and it is very important for apoptosis (39). *P53* protein is the downstream transcription factor of *p38*, and mainly acts to cause programmed apoptosis, and negatively regulate cell division and proliferation. It has been found that up-regulation of *p53* expression can induce tumor cell

Table 3 Free binding energy and RMSD of the key active components of CDDP and key targets

Component	Target	Free binding energy (kcal/mol)	RMSD
Luteolin	<i>ATK1</i>	-9	1.379
	<i>IL6</i>	-5.1	1.211
	<i>TP53</i>	-7.7	1.318
Quercetin	<i>ATK1</i>	-8.9	1.329
	<i>IL6</i>	-5.2	1.618
	<i>TP53</i>	-7.5	1.186
Tanshinone IIa	<i>ATK1</i>	-10.9	1.855
	<i>IL6</i>	-5.7	1.429
	<i>TP53</i>	-8.1	1.789

RMSD, Root Mean Square Deviation; CDDP, Compound Danshen Dropping Pills; *ATK1*, *AKT* serine/threonine kinase 1; *TP53*, tumor protein P53; *IL6*, interleukin 6.

**Figure 10** Heat map of binding energy (A) and Root Mean Square Deviation (RMSD) (B).

apoptosis, and inhibiting the *p38/p53* pathway can protect the apoptosis of ischemic stroke neurons (40). It was found that many apoptotic neuronal pyramidal cells gather in hippocampal CA1 area after epilepsy, and the expression of the *p53* protein increased in pyramidal cells. However, CDDP also have some limitations. Individual patients will have skin rash, dyspnea, decreased blood pressure, and even shock. Long term use may cause stomach pain, indigestion, loss of appetite and other symptoms.

Conclusions

Our research is the first to investigate the underlying

mechanism of cisplatin therapy for epilepsy using web-based pharmacological analysis. The results showed that the multiple pathways, targets, and components of CDDP had synergistic effects in the treatment of epilepsy. Our study can conduct deeper studies upon mechanisms of traditional Chinese medicine treatments for epilepsy, and provides a glimpse into for studying potential mechanisms of TCM treatments in other forms of mental illness using network pharmacology methods. Our study provides a mechanism for CDDP treatment of epilepsy based on the existing database. To guarantee quality and rationality of results, advanced exploratory confirmation *in vivo* and *in vitro* is necessary.

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Footnote

Reporting Checklist: The authors have completed the STREGA reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-195/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-195/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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