Global Journal of Medical Research: a
Neurology & Nervous System
Volume 22 Issue 3 Version 1.0 Year 2022
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Exploring the Mechanism of Tripterygium Wilfordii Treating Epilepsy based on Network Pharmacology

By Yuewang & Xiali
University of Chinese Medicine

Abstract- *Introduction:* This study explored the action mechanism of tripterygium wilfordii active ingredients in the treatment of epilepsy by using network pharmacology.

Methods: TCMSP database was used to screen the active components and genes of Tripterygium wilfordii. On-line text mining server (GeneCards) was used to query epilepsy genes, and the genes of epilepsy and tripterygium wilfordii were standardized and intersected. The mapped genes were imported into Cytoscape software, and the relationship network of "drugs-ingredients-diseases-targets" was obtained. Based on David database, gene ontology (G0) function enrichment analysis and (KEGG) pathway enrichment analysis were performed on the target. And construct KEGG path relation network. On-line database String constructs protein-protein interaction PPI network, and imports relational network layout into Cytoscape software to obtain core sub-network. AutoDockTools and AutoDockVina software are used for molecular docking, and Pymol is used for docking visualization.

Results: There are 21 kinds of active ingredients of Tripterygium wilfordii, including kaempferol, β-sitosterol, triptolide and other active ingredients. 72 cross genes were obtained.

Keywords: *tripterygium wilfordii, epilepsy, network pharmacology.*

GJMR-A Classification: *DDC Code: 616.853 LCC Code: RC372*

Strictly as per the compliance and regulations of:

Exploring the Mechanism of Tripterygium Wilfordii Treating Epilepsy based on Network Pharmacology

Yuewang α & Xiali σ

Abstract- Introduction: This study explored the action mechanism of tripterygium wilfordii active ingredients in the treatment of epilepsy by using network pharmacology.

Methods: TCMSP database was used to screen the active components and genes of Tripterygium wilfordii. On-line text mining server (GeneCards) was used to query epilepsy genes, and the genes of epilepsy and tripterygium wilfordii were standardized and intersected. The mapped genes were imported into Cytoscape software, and the relationship network of "drugs-ingredients-diseases-targets" was obtained. Based on David database, gene ontology (G0) function enrichment analysis and (KEGG) pathway enrichment analysis were performed on the target. And construct KEGG path relation network. On-line database String constructs protein-protein interaction PPI network, and imports relational network layout into Cytoscape software to obtain core sub-network. AutoDockTools and AutoDockVina software are used for molecular docking, and Pymol is used for docking visualization.

Results: There are 21 kinds of active ingredients of Tripterygium wilfordii, including kaempferol, β-sitosterol, triptolide and other active ingredients. 72 cross genes were obtained. Through pathway construction and enrichment analysis, it was found that the potential mechanism may be related to cell proliferation, differentiation, apoptosis, GABA-mediated pathway and so on. The docking results showed that the binding energies of the core targets were all small-5 kcal mol-1, which indicated that there was a good affinity between genes and components.

Conclusion: Tripterygium wilfordii has the characteristics of multi-components, multi-targets and multi-pathways in treating epilepsy. It provides theoretical basis and basis for new drug development and experimental research.

Keywords: tripterygium wilfordii, epilepsy, network pharmacology.

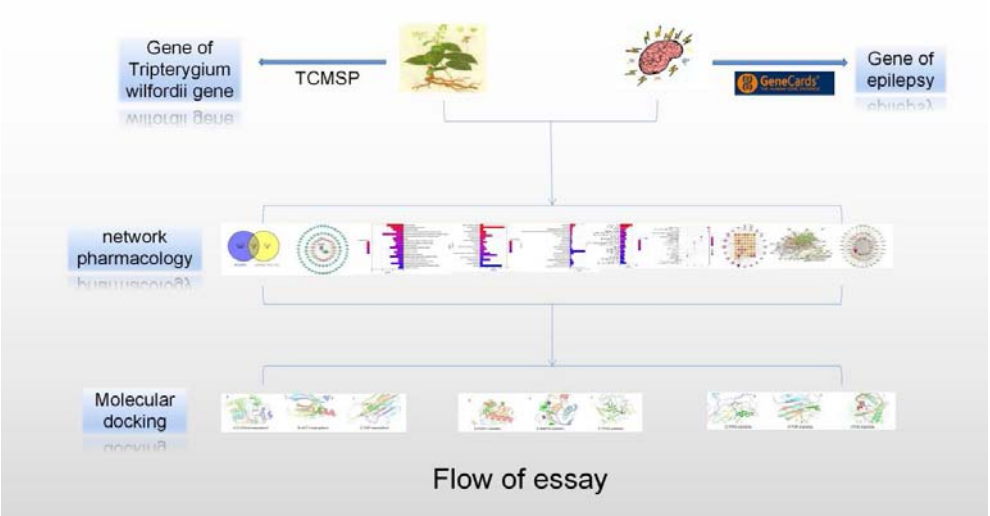
I. Introduction

Epilepsy is one of the most common chronic brain diseases affecting more than 70 million people all over the world. It greatly affects the quality of life of patients and poses a serious threat to their health [1-2]. At present, antiepileptic drug therapy is the most important clinical treatment scheme. Although it can alleviate the symptoms of patients, it can't inhibit the development of epileptic process, and long-term use will also cause various adverse reactions, which will also reduce the drug sensitivity [3]. For short-term clinical seizures of epilepsy, 60% ～ 70% of patients can achieve seizure-free symptoms [4], but there is no satisfactory treatment plan for long-term treatment of epilepsy [5]. Therefore, it is of great clinical significance to develop drugs with high curative effect, good safety and little side effects and new treatment methods.

Traditional Chinese medicine (TCM) is effective in treating epilepsy, with few side effects and wide clinical application. Therefore, this study aims to explore the mechanism of TCM tripterygium wilfordii in treating epilepsy and provide new drug ideas for the treatment of epilepsy. It is a woody vine of Tripterygium wilfordii belonging to Celastraceae. It is cold in nature, bitter in taste and poisonous, and belongs to the four meridians of heart, liver, stomach and kidney. It has the effects of promoting blood circulation, removing blood stasis, clearing away heat and toxic materials, and is distributed in the middle and lower reaches of the Yangtze River [6]. It was first published in Shennong's Materia Medica, and is named Mangcao, which is mainly used for treating scalp wind, carbuncle, breast swelling and hernia [7]; There are detailed records in the Compendium of Materia Medica, which can treat swelling, edema, swelling, jaundice, chronic malaria, poison in the mouth of fish, etc [8]. Studies have shown that triptolide has protective effect on neurons of KA-induced epileptic rats [9]. Moreover, Tripterygium wilfordii polyglycoside can effectively improve the learning and memory ability of epileptic rats induced by PTZ, which is closely related to the up-regulation of Ng and PKC expression levels in hippocampus of rats [10]. Looking at the existing literatures about the effective components of Tripterygium wilfordii, it can be found that there is still a lack of overall and systematic understanding of the anti-epileptic mechanism of Tripterygium wilfordii. In this study, the target of Tripterygium wilfordii was found out through its active ingredients and fused with the epileptic target, and the potential target of Tripterygium wilfordii in treating epilepsy was obtained. The signal pathway or metabolic pathway related to Tripterygium wilfordii in treating

Author α: university of Chinese medicine, Graduate students of TCM college, Changchun, Jilin province, Chaoyang District, China.
e-mail: wangyue032022@163.com
Author σ: Hospital of Changchun University of Chinese Medicine Chief Physician of Center for Encephalopathy, Master tutor, Changchun, Jilin province, Chaoyang District, China.

epilepsy was obtained through function and pathway enrichment analysis, which provided a new idea and direction for comprehensively and systematically expounding the action mechanism of Tripterygium wilfordii in treating epilepsy.



Flow of essay

II. Materials and Methods

a) *Prediction of Active Components and Targets of Tripterygium wilfordii*

The effective components and targets of Tripterygium wilfordii were searched in TCMSP database with keywords "tripterygium wilfordii", "leigongteng" and "thunder god vine". Taking oralbioavail-ability (OB) ≥ 30% and drug-likeness property (DL)≥0.18[11] as screening criteria, the active ingredients of Tripterygium wilfordii were obtained. According to the active components of Tripterygium wilfordii, the corresponding target protein was predicted in TCMSP platform, and then the protein was imported into UniProt database (https://www.Uniprot.org/) for gene standardization.

b) *Prediction of epileptic targets*

Through the online text mining server Genecards (https://www.genecards.org/), the target of epilepsy is predicted, and the data is arranged and duplicated to get the target related to epilepsy.

c) *Prediction of Tripterygium wilfordii's effect on epileptic targets*

The online software Venny2.1 (https://bioinfogp.cnb.csic.es/tools/venny/) was used to intersect the active components of Tripterygium wilfordii with epilepsy-related targets, and the potential targets of the interaction between Tripterygium wilfordii and epilepsy were obtained.

d) *Build a "drug-ingredient-disease-target" relationship network*

After arranging the active ingredients and potential targets of Tripterygium wilfordii, the network of "Tripterygium wilfordii-active ingredients-epilepsy-potential targets" was initially obtained by guiding people to Cytoscape 3.9.0 software for visualization.

e) *Gene Enrichment Analysis*

David database was used to analyze the potential targets by GO and KEGG, and to explore the possible biological function and main signal pathway of Tripterygium wilfordii in treating epilepsy. In this study, the first 20 GO biological functions and KEGG enrichment pathways of enrichment results were selected by using P from small to large as screening conditions.

f) *Construction of "Target -KEGG" Pathway Relationship Network*

Import the KEGG path relationship file into Cytoscape 3.9.0 software, calculate the Degree value, and adjust the size of nodes according to the Degree value, and further obtain the "target -KEGG path" relationship network diagram.

g) *Construction of Protein-Protein Interaction Network (Ppl Network)*

In order to understand the interaction among proteins, the potential targets of Tripterygium wilfordii for epilepsy treatment were input into online database String(https://string_db.org/) to construct a network, and the interaction network between potential target proteins was obtained. The tsv file of PPI network relationship was obtained, and the file was imported into Cytoscape 3.9.0 software for PPI protein interaction analysis. Use plug-in Cyto hubba to screen core targets. Build a core network diagram.

h) *Component-Target Molecule Docking*

Molecular docking of the screened core target and its corresponding active components was carried out to verify the binding activity between components and targets. Firstly, the protein crystal structure of the core target was downloaded from RCSB PDB database

(http://www1.rcsb.org/), and the original ligand and water molecule were removed by PyMol. In addition, the components were introduced into ChemBio3D Ultra for energy minimization. Then, AutoDockTools is used for file conversion before docking, and then AutoDockVina is used for molecular docking. Finally, the sample with the lowest free energy is selected as the docking sample, and it is visualized by PyMol.

III. Results

a) Search the Active Ingredients and Targets of Tripterygium Wilfordii

According to the search conditions, the active components of Tripterygium wilfordii were searched, and 26 kinds of active components of Tripterygium wilfordii were obtained. The structures of the obtained components were verified by Pubchem database, and finally 21 components with complete information were obtained, as shown in Table 1. And its effective active ingredients were input into TCMSP platform to search for 148 targets of active ingredients of Tripterygium wilfordii.

Table 1: Active Ingredients of Tripterygium Wilfordii

ID	Ingredient	OB%	DL
MOL000296	hederagenin	36.91	0.75
MOL000449	Stigmasterol	43.83	0.76
MOL003184	81827-74-9	45.42	0.53
MOL003185	(1R,4aR,10aS)-5-hydroxy-1-(hydroxymethyl)-7-isopropyl-8-methoxy-1,4a-dimethyl-4,9,10,10a-tetrahydro-3H-phenanthren-2-one	48.84	0.38
MOL003196	Tryptophenolide	48.50	0.44
MOL003229	Triptinin B	34.73	0.32
MOL003231	Triptoditerpenic acid B	40.02	0.36
MOL003245	Triptonoditerpenic acid	42.56	0.39
MOL003248	Triptonoterpene	48.57	0.28
MOL003280	TRIPTONOLIDE	49.51	0.49
MOL000358	beta-sitosterol	36.91	0.75
MOL000422	kaempferol	41.88	0.24
MOL004443	Zhebeiresinol	58.72	0.19
MOL002058	40957-99-1	57.20	0.62
MOL003209	Celallocinnine	83.47	0.59
MOL003217	Isoxanthohumol	56.81	0.39
MOL005828	nobiletin	61.67	0.52
MOL003187	triptolide	51.29	0.68
MOL003208	Celafurine	72.94	0.44
MOL003224	Tripdiotolnide	78.72	0.72
MOL003225	Hypodiolide A	76.13	0.49

b) Potential Targets of Tripterygium Wilfordii in the Treatment of Epilepsy

6007 targets related to epilepsy were retrieved. 3170 epileptic targets with a probability greater than or equal to 0.5 were selected, and the acquired tripterygium wilfordii targets and epileptic targets were standardized in Uniprot database. Using software venny2.1, 148 targets with tripterygium wilfordii active ingredients and 3170 epileptic-related targets were mapped and crossed, and 72 potential targets with tripterygium wilfordii for epilepsy treatment were obtained as a result, as shown in Figure 1.

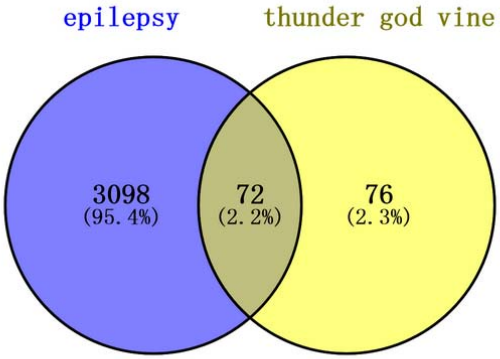


Figure 1: Map of Tripterygium wilfordii epilepsy target. Blue circle represents Tripterygium wilfordii epilepsy target, yellow circle represents epilepsy target, and gray ellipse represents potential tripterygium wilfordii epilepsy target.

c) *Construction of "Drug-Ingredient-Disease-Target" Network*

After the intersection, the potential targets were introduced into Cytoscape 3.9.0 software, and a "drug-component-disease-target" relationship network was constructed. It was found that each component was closely related to epilepsy through genes, as shown in Figure 2. The line segments among various factors represent the interaction relationship, and the more line segments, the stronger the interaction relationship.

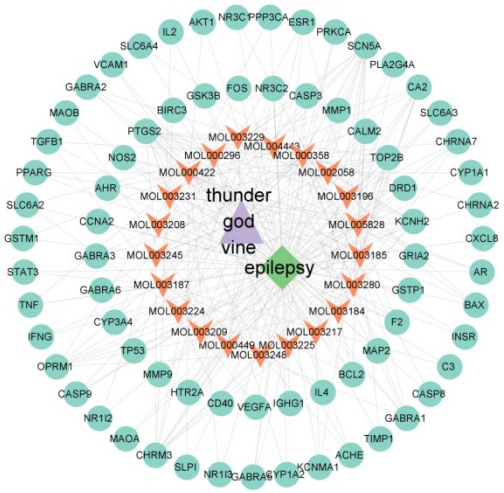


Figure 2: Green circle represents the target, orange inverted V represents the active ingredient of Tripterygium wilfordii, green diamond represents epilepsy, and purple represents Tripterygium wilfordii.

d) *GO Function Enrichment Analysis and KEGG Pathway Enrichment Analysis*

The functional enrichment of GO is mainly divided into three parts: biological process (BP), cellular component (CC) and mo1ecular function (MF). According to the order of P value, the first 20 enrichment items are selected respectively. Among them, the mechanism of tripterygium wilfordii in treating epilepsy mainly involves biological processes such as GABA signaling pathway, cell composition such as synapse, mitochondria and plasma membrane raft, and molecular functions such as steroid binding, protease binding, protein binding, gated ion channel activity and GABA-A receptor activity. See Figure 3- Figure 5 for specific GO comments.

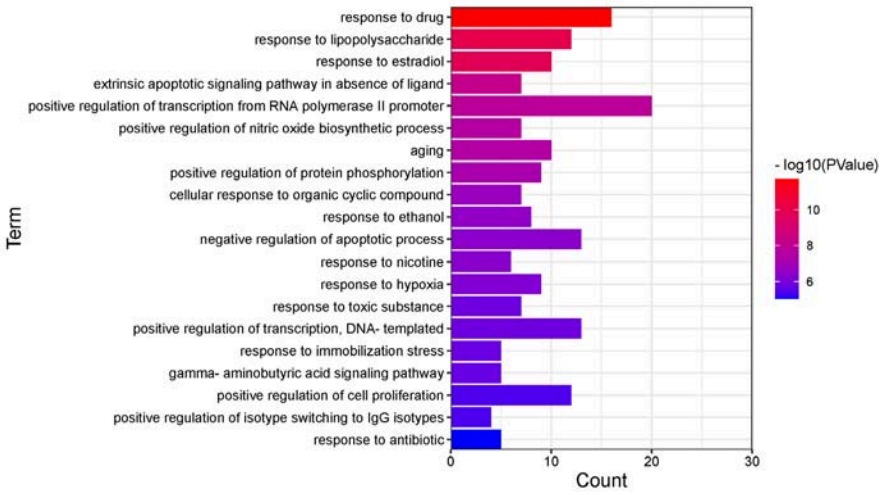


Fig. 3: GO-BP Enrichment Pathway

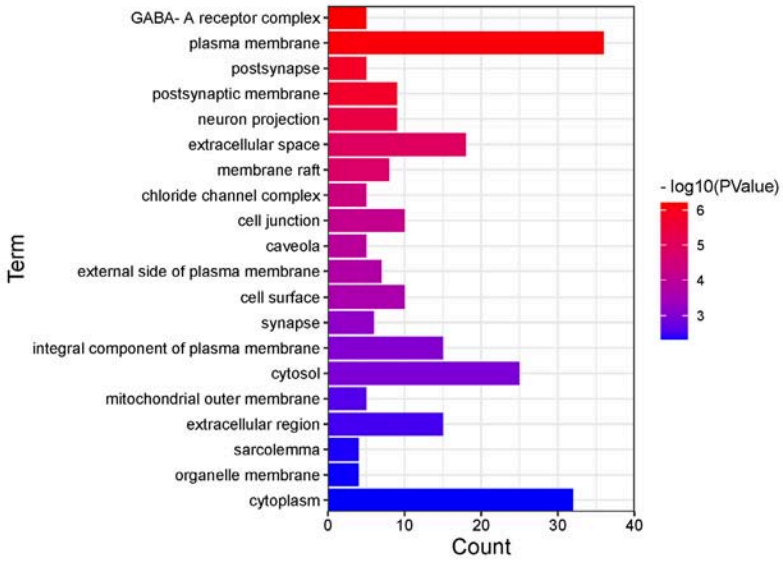


Fig. 4: GO-CC Enrichment Pathway

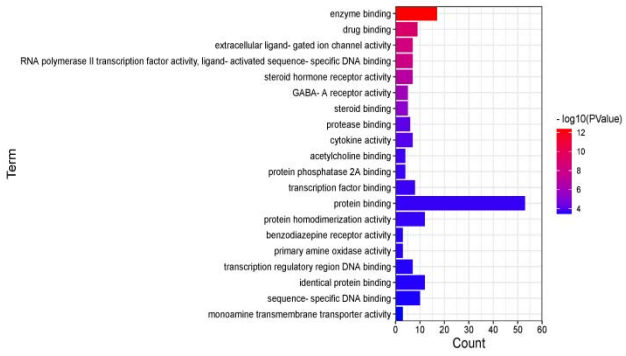


Fig. 5: GO-MF Enrichment Pathway

The enrichment results of KEGG pathway mainly include: cancer pathway, lipid and atherosclerosis signaling pathway, platinum resistance signaling pathway, Kaposi's sarcoma-associated herpes virus infection signaling pathway, chemical carcinogenesis-receptor activation signaling pathway, human cytomegalovirus infection signaling pathway, IL-17 signaling pathway, AGE-RAGE signaling pathway in diabetic complications, fluid shear stress and atherosclerosis signaling pathway, pulmonary tuberculosis signaling pathway, dopaminergic synapse and neuroactive ligand-. See Figure 6- Figure 7.

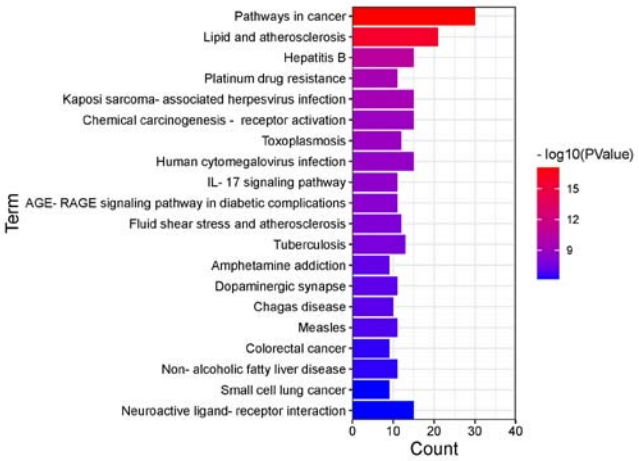


Fig. 6: The enrichment of KEGG pathway and the gradual change from red to blue represent the increasing P value

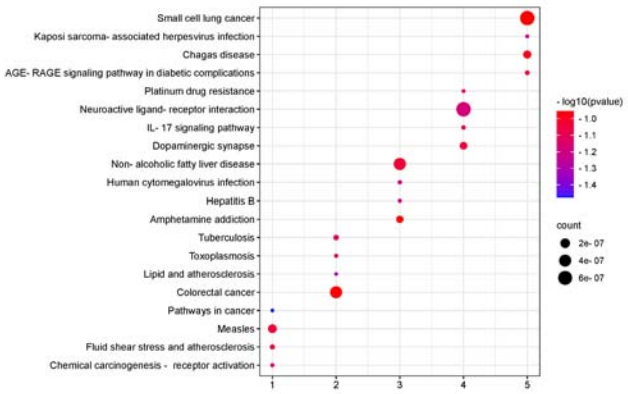


Fig. 7: KEGG bubble diagram. The larger the circle, the more genes are enriched, and the darker the red color, the lower the P value.

e) Build KEGG Channel Relationship Network

Calculate the degree values of the first 20 enriched KEGG pathways and potential targets by using Cytoscape3.9.0 software, and adjust the size and color of the nodes with the degree values to construct the "target -KEGG pathway" relationship network diagram, as shown in Figure 8. Results It was found that Tripterygium wilfordii might play a therapeutic role on epilepsy through multiple active ingredients, multiple targets and multiple ways.

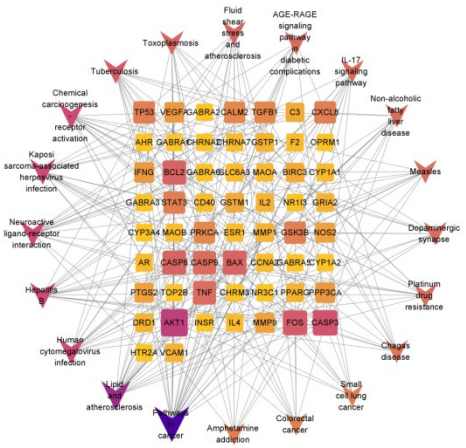


Fig. 8: Purple represents KEGG pathway, the larger the inverted V, the darker the color, the more enrichment pathways, and the larger the square, the darker the color, the more participating pathways.

f) PPI Network Construction and Core Target Prediction

The 72 potential targets of tripterygium wilfordii and epilepsy are entered into the String database, and the PPI relationship network diagram is shown in Figure 9. The results showed that there were direct or indirect interactions among potential targets. The PPI network consisted of 72 nodes and 562 edges, with an average node degree of 15.8. The interaction results of PPI protein showed that protein domain and GABA receptor were found in its features, and it was speculated that Tripterygium wilfordii might play a role in epilepsy through GABA receptor system. Use Cyto hubba plug-in to screen out the core targets among potential targets and obtain the core sub-network. See figure 10. There are eight core targets in the core network, such as AKTI, ESR1, TP53, FOS, CYP3A4, MMP9, TNF and CASP3. These targets are also important targets in KEGG relationship network, and they play an important role not only in KEGG relationship network, but also in PPI network.

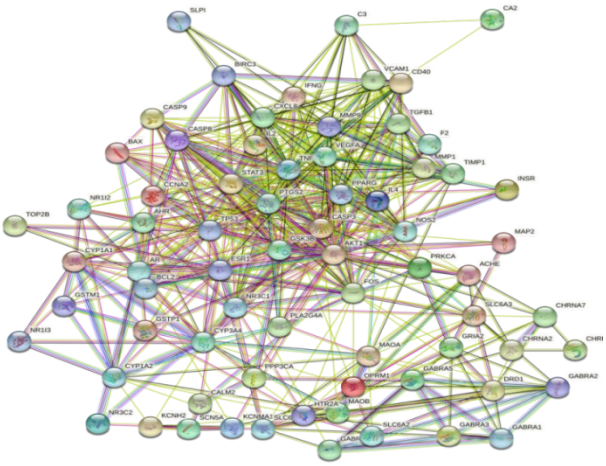


Fig. 9: PPI protein interaction network diagram, the sphere represents the target, the connection between the targets represents the interaction, and the more line segments, the stronger the effect.

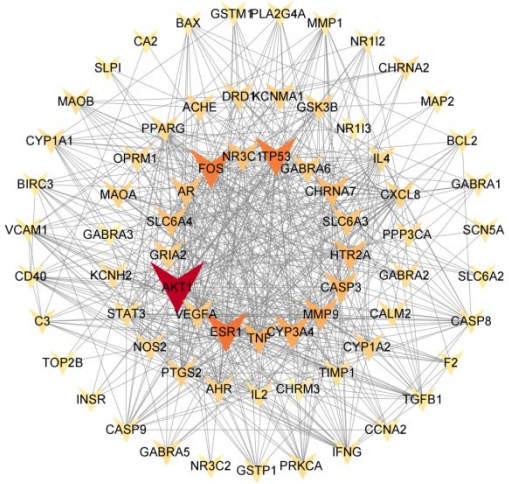


Figure 10: Core Target Map

g) Component-Target Molecule Docking

According to the above screening steps, the related core genes were obtained, and the core genes were molecular docked with the components. The results are shown in Table 2. It was found that all the other core genes can be docked except CASP3 gene, and the binding energy is less than-5 kcal mol-1, which indicates that the core targets have good binding activity with the corresponding active components. The smallest binding energy of the core target is the docking of CYP3A4 with kaempferol, and the binding energy is-

8.39 kcal mol-1. The results show that tripterygium wilfordii can treat epilepsy through gene regulation components and action pathways. The docking mode was visualized by PyMol, and it was found that there were hydrogen bonding forces in these docking structures, which also indicated that the spatial matching degree of components and proteins was good. As shown in Figure 11.

Table 2: Docking information of core target molecules, in which the binding energy unit is kcal mol-1.

Number	Gene name	Ingredient	Docking position	Binding energy
1	AKT1	kaempferol	SER-56、GLN-61、GLN-59	-6.8
2	ESR1	Isoxanthohumol	ASP-21	-7.95
		nobiletin	HIS-206、TYR-213	-7.43
3	MMP9	nobiletin	ALA-191、GLN-227	-7.58
4	TP53	triptolide	ARG-267	-7.57
		nobiletin	GLY-154	-6.61
5	TNF	kaempferol	ALA-134、ASN-46、TRP-28、GLY-24、ILE-136	-6.78
		triptolide	ALA-134、TRP-28、LEU-26	-7.46
6	FOS	triptolide	DA-5010、DC-5011	-8.32
7	CYP3A4	kaempferol	GLU-234、ARG-106	-8.39

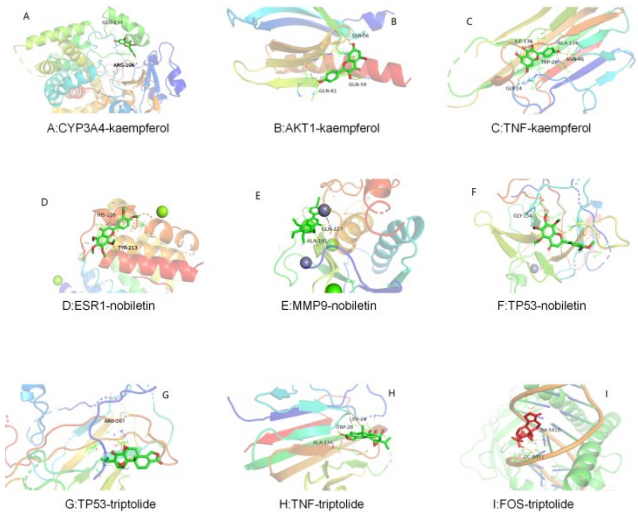


Fig. 11: Molecular Docking Diagram

IV. Discussion

Epilepsy is a serious neurological disease caused by the disorder of the physiological structure or function of the brain. More than half of the patients with epilepsy have one or more complications [12]. Mental diseases (such as depression, anxiety, psychosis, autism) and physical diseases (such as type 1 diabetes, arthritis, peptic ulcer, chronic obstructive pulmonary disease) are all related to long-term seizures [2]. However, the long-term use of antiepileptic drugs has great adverse reactions, and about 50% of patients can't control seizures well by using only one antiepileptic drug [13]. A large number of experiments and clinical studies show that the effect of integrated traditional Chinese and western medicine on epilepsy is better than that of chemical medicine alone [14]. Chinese medicine believes that epilepsy is closely related to pathological factors such as wind, blood stasis, phlegm and fire. The treatment should distinguish the attack period from the recovery period, and grasp the principle of "treating the target when it is urgent, and treating the root when it is slow". In the recovery period, the treatment is mainly to soothe the liver and regulate qi, strengthen the spleen and soothe the nerves, and replenish qi and nourish yin [15]. Finding new drugs to treat epilepsy is our constant pursuit. In recent years, network pharmacology of traditional Chinese medicine (TCM) with "multi-component targeted network" as its main research mode has become increasingly popular, which mainly reveals the drug-gene-disease network relationship by predicting the targeted distribution and pharmacological effects of TCM compounds. Based on the concept of multi-component, multi-target and multi-way action of traditional Chinese medicine, this study studied the main components, targets, biological functions and signal

pathways of Tripterygium wilfordii through network pharmacology technology, in order to reveal its mechanism of action in treating epilepsy.

In this study, 21 kinds of active components and 72 potential anti-epileptic targets of Tripterygium wilfordii were screened by network pharmacology technology, and the network of "drug-component-disease-target", "target -KEGG" and "PPI network" were constructed. Eight core targets including AKTl, ESR1, TP53, FOS, CYP3A4, MMP9, TNF and CASP3 were screened out. The same active ingredient of Tripterygium wilfordii can act on multiple targets; The same signal pathway can enrich multiple targets; The same target can correspond to multiple active ingredients and participate in multiple signal pathways.

The results of network analysis show that tripterygium wilfordii mainly includes kaempferol, β-sitosterol, lignan, triptolide, tripterygium wilfordii polyglycoside and other active components as potential components for treating epilepsy. Studies have shown that flavonoids have antioxidant effect and can protect cells from oxidative stress. This study includes kaempferol, a flavonoid compound. Kaempferol can combine with benzodiazepines on GABA-A receptor to protect the brain from oxidative stress and has anti-epileptic effect [16]. Tripterygium wilfordii can protect neurons from apoptosis induced by kainic acid in rats by inhibiting the expression of MHC- ⅰ , ⅱ molecules in microglia and immune response [17]. Tripterygium wilfordii can also down-regulate the expression of caspase-3 and caspase-9 proteins in hippocampus of epileptic rats induced by kainic acid, thus inhibiting neuronal apoptosis [18]. Tripterygium wilfordii can inhibit neuronal apoptosis in epileptic rats by up-regulating Bcl-2 and down-regulating Bax protein expression [19]. Tripterygium wilfordii extract can inhibit the activation and proliferation of microglia, and its molecular mechanism may be related to the down-regulation of NF-KB protein and mRNA expression in microglia [20]. According to related research, β -sitosterol has obvious anticonvulsant effect among the main active components of Tripterygium wilfordii [21-22]. Experiments have proved that β -sitosterol has neuroprotective effect on hippocampal neurons with epileptic discharge [23]. The latest research found that the mechanism of tripterygium wilfordii polyglycoside inhibiting inflammatory factors may be related to MAPK signal transduction pathway and VEGF signal transduction pathway. Neuroinflammation and oxidative stress are closely related to epilepsy. Some effective anti-inflammatory and antioxidant drugs in animal models have been applied clinically, and have shown therapeutic effects on epilepsy patients.

Both PPI core targets and enrichment pathways confirm that the main components of Tripterygium wilfordii may be related to target regulation. Neuron-activated biomarker protein kinase subtype B 1(Aktl) is a serine/threonine kinase activated by oxidative stress, which is closely related to seizures [24-25]. It can participate in protein synthesis in hippocampal synaptic plasticity and control many pathological signal processes of epilepsy. Therefore, intervention of Akt/MTOR pathway with AKT subtype specific inhibitors may provide a way for the treatment of epilepsy. In addition, the level of interleukin-6(IL-6), a pro-inflammatory cytokine, was confirmed to increase significantly after epilepsy [27-29]. The level of cysteine aspartic protease 3 (Caspas3) encoded by CASP3 was also confirmed to be significantly increased in the serum of epileptic patients [30]. It was found that the expression of miRNA-141 in epileptic patients was up-regulated, which induced neuronal apoptosis and increased the expression level of Caspase-3/9 and p53 protein. miRNA-141 was involved in epilepsy by targeting p53 to inhibit apoptosis [31]. VEGFA is over-expressed in patients with drug-resistant temporal lobe epilepsy, suggesting that it is involved in the pathological process of epilepsy [32]. Seizures significantly inhibit the plasticity of synapses, and the short-term plasticity mainly depends on the fluctuation and steady state of calcium levels in synapses [33]. The neuroprotective effect of ESR1 is mainly through its influence on synaptic plasticity [34]. ZHANG et al. [35] found that mice lacking FOS expression had more severe seizures, increased neuronal excitability and neuronal cell death, and FOS regulated the expression of GLUR6 and brain-derived neurotrophic factor (BDNF) in vivo and in vitro. As an important factor of apoptosis after brain injury, HIF-1a may provide a new target for the treatment of epilepsy [36]. Under hypoxia, HIF-1a is widely expressed in neurons, glial cells and ependymal cells in the central nervous system. Li Yanmei [37] and others found that the homozygous mutation of CYP3A4*1G may be related to drug resistance in children with epilepsy with hereditary or unknown etiology. Screening CYP3A4*1G genotype is one of the important methods to guide the selection of antiepileptic drugs and to judge and predict the therapeutic effect of antiepileptic drugs in children with hereditary or unknown etiology. Liu Dandan [38] studies have shown that seizures in the acute stage of viral encephalitis are related to the increased levels of IL-1β, IL-6 and TNF-α in cerebrospinal fluid. Therefore, the core target of this study is closely related to regulating the occurrence and development of epilepsy treated by effective components of Tripterygium wilfordii.

In order to further analyze the signal pathways and biological processes involved in tripterygium wilfordii therapeutic targets, the KEGG signal pathways and GO biological processes of tripterygium wilfordii therapeutic targets were enriched. Among them, oxidative stress and neuronal apoptosis are both related to seizures. There is evidence that in some animal

epilepsy models, antioxidant therapy can reduce the nerve damage caused by oxidative free radicals, thus playing an anti-epileptic role [39-40]. At present, most antiepileptic drugs play an antiepileptic role mainly by regulating voltage-gated ion channels, enhancing C-aminobutyric acid-mediated inhibition, regulating synaptic release, or blocking ionic glutamate receptors. Therefore, the function of synapses is closely related to epilepsy [41]. It has also been reported that the level of catecholamine in striatum decreased during the incubation period in the seizure model induced by sodium glutamate [42]. The activity of neurotransmitter receptor is also closely related to the occurrence of epilepsy. It has been found that stimulating vagus nerve can enhance the activity of inhibitory neurotransmitter receptor a- aminobutyric acid receptor, thus inhibiting the occurrence of epilepsy [43]. The results of G0 bioaccumulation analysis in this paper provide bioinformatics basis for potential target therapy of epilepsy predicted by Tripterygium wilfordii. The results of KEGG enrichment analysis showed that Tripterygium wilfordii might be related to epilepsy through IL-17 signaling pathway, human cytomegalovirus infection and tumor necrosis factor signaling pathway. The above reports on the effective active ingredients of Tripterygium wilfordii are basically consistent with the predicted results of the enrichment analysis of Tripterygium wilfordii target and KEGG signal pathway and GO biological process in this study.

V. Conclusion

The selected targets, their biological functions and enriched signal pathways are closely related to the regulation of biological changes of epilepsy. However, many components selected from Tripterygium wilfordii are regulated by the core targets, which play a role in treating epilepsy. Further, it is suggested that the active ingredients of Tripterygium wilfordii may exert its therapeutic effect by acting on a variety of biological changes in the development of epilepsy. Its core target is closely related to the development of epilepsy, and the biological functions and enriched signal pathways of potential targets are also closely related to the mechanism of epilepsy. This study preliminarily expounded the molecular mechanism of tripterygium wilfordii in treating epilepsy, which provided a theoretical basis for new drug research and a new idea for treating epilepsy with traditional Chinese medicine.However, further experimental verification is still needed.

Author Contributions

X.L.and Y.W. participated in the design of this study, and they both performed the statistical analysis. X.L.carried out the study and collected important background information. Y.W.drafted the manuscript. All authors read and approved the final manuscript. X.L.and Y.W. carried out the concepts, design.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

First of all, I would like to thank my alma mater, Changchun University of Traditional Chinese Medicine, and then I would like to thank Mr. Li Wannan for his suggestions on this research.

Data availability

The data used to support the findings of this study is available from the corresponding author upon request.

References Références Referencias

1. Dursun, et al. "Using predictive analytics to identify drug-resistant epilepsy patients. " Health informatics journal (2019).
2. "Treatment Strategy for Adult Epilepsy : A Current Approach." brain\&\nerve: 67(2015):1043-1049.
3. Li, Qinrui , et al. "Alterations of apoptosis and autophagy in developing brain of rats with epilepsy: Changes in LC3, P62, Beclin-1 and Bcl-2 levels. " Neuroscience Research (2017):S016801 02173 03 012.
4. Scheffer, Ingrid E , et al. "ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology." Epilepsia 58.Suppl.(2017):512.
5. Cerri, C. , M. Caleo , and Y. Bozzi . "Chemokines as new inflammatory players in the pathogenesis of epilepsy." Epilepsy Research (2017):77-83.
6. Si Jin Ping. "Study on the current situation and sustainable utilization of Tripterygium wilfordii resources." Chinese Herbal Medicine 28.1(2005):2.
7. Shennong Materia Medica [M]. Beijing Academy Press, 2007: 274.
8. Zhao Xuemin. Compendium of Materia Medica [M]. Beijing Chinese Medicine Press, 2015: 217.
9. Pan Xin et al. "Effect of triptolide on the expression of voltage-gated potassium channel kv1.1 in epileptic rats." journal of international neurology and neurosurgery 039.002(2012):108-113.
10. Anonymous. "Effects of Tripterygium wilfordii polyglycoside on learning and memory and expression of Ng and PKC in hippocampus of epileptic rats." Journal of Stroke and Neurological Diseases 34.2(2017):4.
11. Wang, W. , et al. "Study on the multi-targets mechanism of triphala on cardio-cerebral vascular diseases based on network pharmacology." Biomedicine & Pharmacotherapy 116(2019):108 994.

12. "Infections, inflammation and epilepsy." Acta Neuropathologica 131.2(2016):211-234.
13. Verrotti, A. , et al. "Pharmacodynamic interactions of antiepileptic drugs: From bench to clinical practice." Epilepsy & Behavior 104(2020):106939-.
14. Zhou Zhu, and Mao Zhixuan. "Meta-analysis on the efficacy and safety of integrated traditional Chinese and western medicine in the treatment of intractable epilepsy." World Latest Medical Information Digest 86(2019):4.
15. Chen Haimin, and Cao Kegang. "Traditional Chinese Medicine Treatment of Epilepsy." Chinese Journal of Clinicians 47.10(2019):3.
16. Dutra Marina Rascio Henriques, et al."Protective Role of UCP2 in Oxidative Stress and Apoptosis during the Silent Phase of an Experimental Model of Epilepsy Induced by Pilocarpine.." Oxidative medicine and cellular longevity 2018.(2018). doi:10.1155/2018/6736721.
17. Lu Yao et al. "Effect of triptolide on expression of MHC molecules in rat brain microglia induced by kainic acid." Journal of Liaoning University of Traditional Chinese Medicine 14.9(2012):3.
18. Yang Yicheng et al. "Effect of triptolide on caspase3 and caspase9 protein expression in neurons of rats with epilepsy induced by kainic acid." Journal of Liaoning University of Traditional Chinese Medicine 15.2(2013):3.
19. Yang Yicheng et al. "Protective effect of triptolide on hippocampal neuron apoptosis in epileptic rats." China Pharmacy 24.27(2013):3.
20. Song Yanli et al. "Effect of triptolide on NF-κB expression in BV-2 microglia activated by kainic acid." Journal of Liaoning University of Traditional Chinese Medicine 16.10(2014):3.
21. Xiao Zhibin, Jia Hanxue, and Liu Xiaolei. "Research status of pharmacological activity of β-sitosterol." World Latest Medical Information Digest 8(2015):3.
22. Liu Weiliang, Ji Yu, and Huang Aixiang. "Research and development progress of β-sitosterol." Agricultural Products Processing 1(2019):4.
23. Dong Xue et al. "Toxicity of β-sitosterol to primary rat hippocampal neurons." Heilongjiang Medical Science 36.4(2013):2.
24. Tenney, J. R. et al. "Cerebral glucose hypometabolism is associated with mitochondrial dysfunction in patients with intractable epilepsy and cortical dysplasia." Epilepsia 55.9(2015):1415-1422.
25. Lin, Y. X. , et al. "PI3K-AKT pathway polymerase chain reaction (PCR) array analysis of epilepsy induced by type II focal cortical dysplasia." Genetics and molecular research: GMR 14.3(2015):9994-10000.
26. Rrv, A, et al. "Phosphoproteomic analysis reveals Akt isoform-specific regulation of cytoskeleton proteins in human temporal lobe epilepsy with hippocampal sclerosis - ScienceDirect." Neurochemistry International 134.
27. Ta, A, et al. "The production of IL-6 in acute epileptic seizure: A video-EEG study - ScienceDirect." Journal of Neuroimmunology 316(2018):50-55.
28. Yu, Q. , M. W. Zhao , and P. Yang . "LncRNA UCA1 Suppresses the Inflammation Via Modulating miR-203-Mediated Regulation of MEF2C/NF-κB Signaling Pathway in Epilepsy." Neurochemical Research 45.4(2020).
29. Vries, Eed , et al. "Inflammatory mediators in human epilepsy: A systematic review and meta-analysis." Neuroscience & Biobehavioral Reviews 63(2016).
30. Josi, A. , et al. "Depressive, inflammatory, and metabolic factors associated with cognitive impairment in patients with epilepsy." Epilepsy & Behavior 86(2018):49-57.
31. Ding, et al. "Suppression of microRNA-141 suppressed p53 to protect against neural apoptosis in epilepsy by SIRT1 expression. " Journal of Cellular Biochemistry (2018).
32. JL Castañeda-Cabral, et al. "Increased protein expression of VEGF-A, VEGF-B, VEGF-C and their receptors in the temporal neocortex of pharmacoresistant temporal lobe epilepsy patients." Journal of Neuroimmunology (2018).
33. Chen, Yuan Hao , et al. "Profound deficits in hippocampal synaptic plasticity after traumatic brain injury and seizure is ameliorated by prophylactic levetiracetam." Oncotarget 9.14(2018).
34. Sheng Lei et al. "Network Pharmacological Study of Chaihu Shugan Powder in Treating Post-stroke Depression." Chinese Herbal Medicine 49.15(2018):7.
35. Zhang, J. et al. "c-fos regulates neuronal excitability and survival. " Nature Genetics 30.4(2002):416.
36. Jie, L. , et al. "Altered expression of hypoxia-Inducible factor-1α participates in the epileptogenesis in animal models." Synapse (2014).
37. Li Yanmei. Analysis of CYP3A4 gene polymorphism in children in southwest China and study on the correlation between drug-resistant epilepsy. Diss. Chongqing Medical University, 2012.
38. Liu Dandan. Study on the relationship between seizures in acute phase of viral encephalitis and the expression levels of IL-1β, IL-6 and TNF-α in serum and cerebrospinal fluid. Diss. Shanxi Medical University.
39. Aguiar Carlos Clayton Torres, et al."Oxidative stress and epilepsy: literature review.." Oxidative medicine and cellular longevity 2012.(2012). doi:10.1155/2012/795259.
40. Henriques, Dmr , et al. "Protective Role of UCP2 in Oxidative Stress and Apoptosis during the Silent

Phase of an Experimental Model of Epilepsy Induced by Pilocarpine." Oxidative medicine and, cellular longevity 2018(2018):1-12.
41. Löscher Wolfgang, et al. "Synaptic Vesicle Glycoprotein 2A Ligands in the Treatment of Epilepsy and Beyond." Cns Drugs 30.11(2016):1055-1077.
42. Vega, et al. "Effect of gamma-ethyl-gamma-phenyl-butyrolactone (EFBL), anticonvulsant and hypnotic drug, on mouse brain catecholamine levels." Acta pharmaceutica: a quarterly journal of Croatian Pharmaceutical Society and Slovenian Pharmaceutical Society, dealing with all branches of pharmacy and allied sciences (2017).
43. Zhang, X. , and X. Yan . "The study of activities of neurotransmitter of thalami by vagus nerve stimulation in epileptic rats." Stroke and Nervous Diseases (2003).