RESEARCH ARTICLE

Exploring the comorbidity mechanism of Chaihu Jia Longgu Muli Decoction in the treatment of vertigo and anxiety disorder based on network pharmacology and molecular docking

Hanshuo Dong[1], Bin Zhang[2], Xin Teng[2], Li Sun[1,*]

[1]Dizziness Clinic, Jilin Provincial Academy of Chinese Medicine Sciences, Changchun, Jilin, China. [2]Changchun University of Chinese Medicine, Changchun, Jilin, China.

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The incidence of vertigo with anxiety has been increasing year by year. Vertigo with anxiety significantly affects the physical and mental health of patients and reduces their quality of life. Therefore, how to effectively treat this condition has attracted widespread attention. This study investigated the mechanism of Chaihu Jia Longgu Muli Decoction (CLMD) in treating the co-morbidities of vertigo and anxiety utilizing network pharmacology and molecular docking technology. The active ingredients and action targets of CLMD were obtained from the TCMSP, BATMAN-TCM, HERB databases. The disease targets for vertigo disease and anxiety disorder were acquired using Genecard, OMIM, and DRUGBANK databases. These data sources were integrated and analyzed to identify the key action targets for the co-treatment of heterogeneous diseases by CLMD. The network visualization and STRING mapping of the protein interaction network were performed using Cytoscape v3.8.2. Additionally, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were conducted using Metascape platform. The molecular docking was verified using AutoDock. A total of 100 effective active ingredients were obtained from CLMD. Among these, 262 potential targets were predicted with 101 key targets being identified as exerting therapeutic effects. The notable targets included AKT1, IL6, TNF, VEGFA, IL1B, and others. The GO and KEGG databases were primarily utilized to investigate the involvement of these active ingredients and targets in various signaling pathways including 5-hydroxytryptaminergic synapses, dopaminergic neural synapses, cAMP signaling pathways, calcium signaling pathways. The molecular docking analysis revealed a strong binding affinity between the active ingredients and the crucial target molecules. Network pharmacological analysis further elucidated that CLMD exerted its therapeutic effects on the co-occurrence of vertigo and anxiety through diverse biological processes and associated signaling pathways. These findings contributed valuable insights into the underlying mechanism of CLMD in the treatment of vertigo and anxiety co-morbidities.

Keywords: vertigo; anxiety disorders; Chaihu Jia Longgu Muli Decoction; network pharmacology.

[*]**Corresponding author:** Li Sun, Dizziness Clinic, Jilin Provincial Academy of Chinese Medicine Sciences, Changchun 130000, Jilin, China. Email: 18946584555@163.com.

Introduction

Vertigo is a form of movement illusion resulting from a spatial orientation disorder within the human body with a potential lifetime prevalence reaching up to 10% [1]. In conjunction with vertigo symptoms, a considerable number of patients also experience comorbidities such as

anxiety, depression, and other psychological ailments [2]. Anxiety disorder is one of the most common accompanying symptoms of vertigo, seen in 18% of these patients [3]. The intricate association between vertigo and anxiety engenders a reciprocal causation, resulting in a detrimental cycle that significantly impacts patients' quality of life. The advancement of psychosomatic medicine has prompted an increasing number of scholars to recognize the significance of psychological factors in disease pathogenesis, consequently making vertigo accompanied by anxiety disorder a prominent subject of research both domestically and internationally.

Traditional Chinese medicine (TCM) has a long history of treating diseases and has formed its unique treatment system during thousands of years of clinical practice. One of the most important elements of TCM is to treat different diseases with the same treatment. Chaihu Jia Longgu Muli Decoction (CLMD) is a classic TCM formula, which is first recorded in the “Treatise on Febrile Diseases” and has the effect of reconciling heat, calming, and tranquilizing [4]. Clinical treatment of vertigo with anxiety disorder shows that CLMD has a remarkable effect on anxiety disorder [5]. Related studies have confirmed that CLMD treats mental and nervous system diseases by regulating monoamine transmitters, brain-derived neurotrophic factors, and anti-apoptosis [4-7]. In extensive clinical experience, CLMD has been found that it is effective in treating vertigo with anxiety. However, it is important to note that the composition of this formula is complex, which makes it difficult to explain the mechanism of action using a single clinical study. Notably, there is a dearth of scholarly exploration regarding the effectiveness and underlying mechanism of action for these two concurrent conditions. Network pharmacology, encompassing various interdisciplinary fields such as systems biology, pharmacology, and bioinformatics, enables the comprehensive analysis of compounds and diseases through the exploration of disease-gene-target-drug interaction networks. This approach offers notable advantages in elucidating the targets and mechanisms underlying drug treatment for various diseases.

This study employed network pharmacology and molecular docking techniques to investigate the underlying mechanism of CLMD in treating the co-occurrence of vertigo and anxiety. The research would offer insights for the clinical utilization of CLMD in managing vertigo patients with comorbid anxiety.

Materials and methods

Screening of related ingredients and targets of CLMD

The chemical constituents of CLMD included Radxi bupleuri, Rheum officinale, Pinellia ternate, Scutellaria baicalensis, Ginseng, Cassia twig, Ginger, Poria cocos, Long Gu, Conchaostreae, and Fructus ZIziphi Jujubae and were identified through the utilization of TCMSP (http://tcmspw.com/tcmsp.php), BATMAN-TCM (http://bionet.ncpsb.org.cn/batman-tcm/), and the HERB database (http://herb.ac.cn/). The TCMSP database was screened using constraints of oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18. The potential active components of BATMAN-TCM database were obtained by applying a score cutoff of ≥ 20 and a *P* value less than 0.05. The active ingredients and targets were supplemented using the HERB, Swiss Target Prediction database (http://swisstargetprediction.ch/), and relevant literatures, and then unified, sorted, and removed duplicates to establish a target database for core prescriptions. Standardized naming was achieved through the utilization of the Uniprot (https://www.uniprot.org/) database.

Disease target screening

Vertigo and anxiety disorder related genes were identified from the databases of Genecard (http://www.genecards.org/), OMIM (http://www.omim.org/), and DRUGBANK (https://go.drugbank.com/). The Genecard

database was assessed based on the median value of its "relevance score". Following the integration of the three databases, redundant targets were excluded to establish a comprehensive disease target database.

Looking for the target of CLMD in the treatment of vertigo with anxiety

The Venny 2.1 (https://bioinfogp.cnb.csic.es/tools/venny/) was employed to combine the target of CLMD with the target of vertigo and anxiety disorder. The common target of CLMD was a potential target for the treatment of comorbid vertigo and anxiety.

Construction of PPI network and TCM-component-target-disease network

The drug-disease common targets were entered into the String database (https://string-db.org/) with the species specified as "Homo sapiens" and the confidence level of 0.4. The protein-protein interaction (PPI) network was employed. Cytoscape 3.8.2 (http://www.Cytoscape.org/) was used to further visualize the results of the PPI network. The common targets were imported into Cytoscape 3.8.2 to construct "TCM-component-target-disease" network. The network diagram was visualized and analyzed.

Gene ontology (GO) functional enrichment analysis and Kyoto encyclopedia of genes and genomes (KEGG) pathway enrichment analysis

The Metascape database (https://metascape.org/gp/index.html) was used for enrichment of the core target with *P* value less than 0.01. The top 20 biological processes and signaling pathways were screened out.

Molecular docking

To assess the affinity between the active ingredients and targets, the molecular docking of active ingredients of CLMD and core targets was conducted using the AutoDock Vina software (https://vina.scripps.edu/). The 3D structures of ingredients and targets were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and PDB databases (https://www.rcsb.org/). The proteins were processed using PyMol (https://www.pymol.org/) and AutoDock Vina software and stored in qdbqt format. Following molecular docking with AutoDock Vina, PyMol was used to visualize and analyze the complex of the core target protein and the ligand.

Results

CLMD active ingredient target prediction

A total of 120 active ingredients of CLMD were identified through database screening. There were 13 ingredients in Radxi bupleuri, 32 in Scutellaria baicalensis, 11 in Pinellia ternate, 4 in Ginger, 16 in Ginseng, 6 in Cassia twig, 6 in Poria cocos, 7 in Rheum officinale, 2 in Long Gu, 5 in Conchaostreae, 18 in Fructus ZIziphi Jujubae. After removing duplicates, 100 potential active ingredients were obtained (Table 1). Meanwhile, 262 drug targets were obtained from Swiss target prediction database through duplication.

Disease related genes

A total of 5,340 genes related to vertigo and 1,645 genes related to anxiety disorder were obtained from Genecard, OMIM, and DRUGBANK databases. The data were aggregated, and duplicates were removed, resulting in the identification of 2,573 targets for vertigo and 1,474 targets for anxiety disorder.

Potential targets of CLMD in treating vertigo with anxiety disorder

The possible targets of CLMD for the treatment of vertigo with anxiety disorder were shown in Figure 1. A total of 101 common targets between the CLMD active ingredients targets and vertigo with anxiety disorder related targets were identified.

Key targets protein-protein interaction (PPI) analysis

The PPI network map of 101 common targets for CLMD treatment of vertigo with anxiety disorder was constructed (Figure 2). Targets that were situated closer to the center in the PPI map exhibited a higher degree of correlation with

Table 1. Active ingredients of CLMD.

Mol ID	Molecule name	OB (%)	DL
MOL002714	baicalein	33.52	0.21
MOL000358	beta-sitosterol	36.91	0.75
MOL000449	Stigmasterol	43.83	0.76
MOL002670	Cavidine	35.64	0.81
MOL000519	coniferin	31.11	0.32
MOL006957	(3S,6S)-3-(benzyl)-6-(4-hydroxybenzyl) piperazine-2,5-quinone	46.89	0.27
MOL001755	24-Ethylcholest-4-en-3-one	36.08	0.76
MOL005030	gondoic acid	30.7	0.2
MOL006936	10,13-eicosadienoic	39.99	0.2
MOL006967	beta-D-Ribofuranoside, xanthine-9	44.72	0.21
MOL003578	Cycloartenol	38.69	0.78
MOL000098	quercetin	46.43334812	0.27525
MOL000422	kaempferol	41.88224954	0.24066
MOL000354	isorhamnetin	49.60437705	0.306
MOL004609	Areapillin	48.96435072	0.41394
MOL004598	3,5,6,7-tetramethoxy-2-(3,4,5-trimethoxyphenyl) chromone	31.97495927	0.59317
MOL000490	petunidin	30.04553904	0.30712
MOL004653	(+)-Anomalin	46.05534076	0.6566
MOL013187	Cubebin	57.1281289	0.63988
MOL001645	Linoleyl acetate	42.10076623	0.19845
MOL004624	Longikaurin A	47.72214984	0.53015
MOL004718	Pseudo-spinasterol	42.97936552	0.75693
MOL002776	Baicalin	40.12360996	0.75264
MOL000471	aloe-emodin	83.38	0.24
MOL002235	EUPATIN	50.8	0.41
MOL000096	(-)-catechin	49.68	0.24
MOL002281	Toralactone	46.46	0.24
MOL002268	rhein	47.07	0.28
MOL002297	Daucosterol_qt	35.89	0.7
MOL012921	stepharine	31.55	0.33
MOL012946	zizyphus saponin I_qt	32.69	0.62
MOL012976	coumestrol	32.49	0.34
MOL012986	Jujubasaponin V_qt	36.99	0.63
MOL012992	Mauritine D	89.13	0.45
MOL001454	berberine	36.86	0.78
MOL001522	(S)-Coclaurine	42.35	0.24
MOL000211	Mairin	55.38	0.78
MOL004350	Ruvoside_qt	36.12	0.76
MOL000492	(+)-catechin	54.83	0.24
MOL000627	Stepholidine	33.11	0.54
MOL007213	Nuciferin	34.43	0.4
MOL000787	Fumarine	59.26	0.83
MOL002773	beta-carotene	37.18	0.58
MOL000296	hederagenin	36.91	0.75
MOL000273	(2R)-2-[(3S,5R,10S,13R,14R,16R,17R)-3,16-dihydroxy-4,4,10,13,14-pentamethyl-2,3,5,6,12,15,16,17-octahydro-1H-cyclopenta[a]phenanthren-17-yl]-6-methylhept-5-enoic acid	30.93	0.81
MOL000275	trametenolic acid	38.71	0.8
MOL000279	Cerevisterol	37.96	0.77
MOL000282	ergosta-7,22E-dien-3beta-ol	43.51	0.72
MOL000283	Ergosterol peroxide	40.36	0.81
MOL004576	taxifolin	57.84	0.27
MOL000359	sitosterol	36.91	0.75
MOL000073	ent-Epicatechin	48.96	0.24
MOL001736	(-)-taxifolin	60.51	0.27
MOL000173	wogonin	30.68	0.23
MOL001689	acacetin	34.97	0.24
MOL002928	oroxylin a	41.37	0.23
MOL000228	(2R)-7-hydroxy-5-methoxy-2-phenylchroman-4-one	55.23	0.2
MOL008206	Moslosooflavone	44.09	0.25
MOL002934	NEOBAICALEIN	104.34	0.44
MOL012266	rivularin	37.94	0.37
MOL002927	Skullcapflavone II	69.51	0.44
MOL000552	5,2'-Dihydroxy-6,7,8-trimethoxyflavone	31.71	0.35

MOL002915	Salvigenin	49.07	0.33
MOL002933	5,7,4'-Trihydroxy-8-methoxyflavone	36.56	0.27
MOL002917	5,2',6'-Trihydroxy-7,8-dimethoxyflavone	45.05	0.33
MOL002932	Panicolin	76.26	0.29
MOL002897	epiberberine	43.09	0.78
MOL002937	DIHYDROOROXYLIN	66.06	0.23
MOL001458	coptisine	30.67	0.86
MOL002909	5,7,2,5-tetrahydroxy-8,6-dimethoxyflavone	33.82	0.45
MOL000525	Norwogonin	39.4	0.21
MOL002914	Eriodyctiol (flavanone)	41.35	0.24
MOL002925	5,7,2',6'-Tetrahydroxyflavone	37.01	0.24
MOL002879	Diop	43.59	0.39
MOL012245	5,7,4'-trihydroxy-6-methoxyflavanone	36.63	0.27
MOL012246	5,7,4'-trihydroxy-8-methoxyflavanone	74.24	0.26
MOL002910	Carthamidin	41.15	0.24
MOL002913	Dihydrobaicalin_qt	40.04	0.21
MOL001490	bis[(2S)-2-ethylhexyl] benzene-1,2-dicarboxylate	43.59	0.35
MOL010415	11,13-Eicosadienoic acid, methyl ester	39.28	0.23
	Calcium Phosphate		
	Calcium Carbonate		
	Aluminum		
	Calcium Sulphate		
	Silicon		
MOL003648	Inermin	65.83	0.54
MOL005344	ginsenoside rh2	36.32	0.56
MOL005384	suchilactone	57.52	0.56
MOL005321	Frutinone A	65.9	0.34
MOL005308	Aposiopolamine	66.65	0.22
MOL005356	Girinimbin	61.22	0.31
MOL005320	arachidonate	45.57	0.2
MOL005317	Deoxyharringtonine	39.27	0.81
MOL005318	Dianthramine	40.45	0.2
MOL005348	Ginsenoside-Rh4_qt	31.11	0.78
MOL005376	Panaxadiol	33.09	0.79
MOL005399	alexandrin_qt	36.91	0.75
MOL006129	6-methylgingediacetate2	48.73	0.32
MOL001771	poriferast-5-en-3beta-ol	36.91	0.75
MOL008698	Dihydrocapsaicin	47.07	0.19

Notes: DL: Drug-like properties. OB: Oral bioavailability.

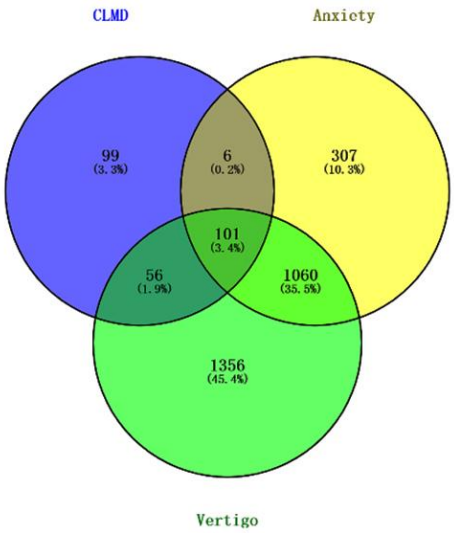

Figure 1. Venny diagram of the targets of CLMD and the targets of vertigo with anxiety disorder.

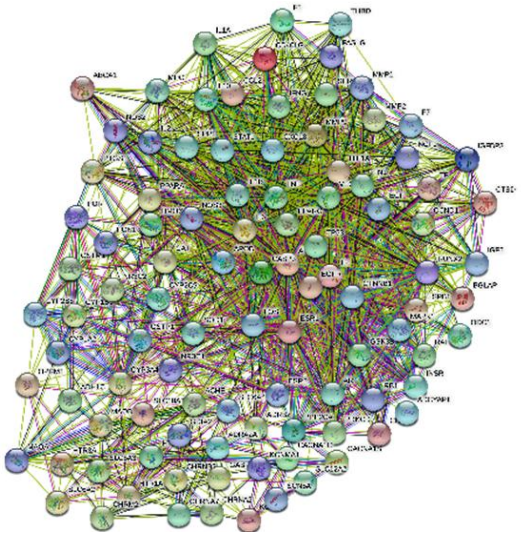

Figure 2. PPI network of the 101 targets of CLMD for the treatment of vertigo with anxiety disorder.

Table 2. Core targets of CLMD for treating vertigo with anxiety disorder.

Uniprot	Gene	Protein	Degree
P31749	*AKT1*	RAC-alpha serine/threonine-protein kinase	65
P05231	*IL6*	Interleukin-6	63
P01375	*TNF*	Tumor necrosis factor	59
P15692	*VEGFA*	Vascular endothelial growth factor A	58
P01584	*IL1B*	Interleukin-1 beta	57
P04637	*TP53*	Cellular tumor antigen p53	56
P01100	*FOS*	Protein c-Fos	54
P42574	*CASP3*	Caspase-3	54
P01133	*EGF*	Pro-epidermal growth factor	53
P03372	*ESR*	Estrogen receptor	52

other targets, suggesting their potential significance in the treatment of vertigo with anxiety by CLMD. There were 101 nodes and 1,363 dges, the average node degree was 27, an average local clustering coefficient of 0.64, and $P < 1.0e-16$. The obtained PPI network data were imported into Cytoscape v3.8.2 software and arranged according to the value of degree. The higher the degree value was, the more important it might be in the treatment of vertigo with anxiety with CLMD. The top 10 targets in degree ranking were *AKT1*, *IL6*, *TNF*, *VEGFA*, *IL1B*, *TP53*, *FOS*, *CASP3*, *EGF*, *ESR*. These targets might be the key to treating vertigo and anxiety comorbidity with CLMD (Table 2).

CLMD-compound-target-disease network map

The active ingredients and targets of CLMD were imported into the Cytoscape v3.8.2 to construct the CLMD-compound-target-disease network, which could more intuitively reflect the characteristics of multi-components and multi-targets of CLMD in the treatment of vertigo and anxiety comorbidities (Figure 3). The degree values were calculated through the Network Analysis plug-in. The top ingredients were determined as quercetin, beta-sitosterol, stigmasterol, kaempferol, and baicalein. The results indicated that these ingredients might be the key active ingredients for the simultaneous treatment of different diseases in CLMD.

GO functional enrichment analysis

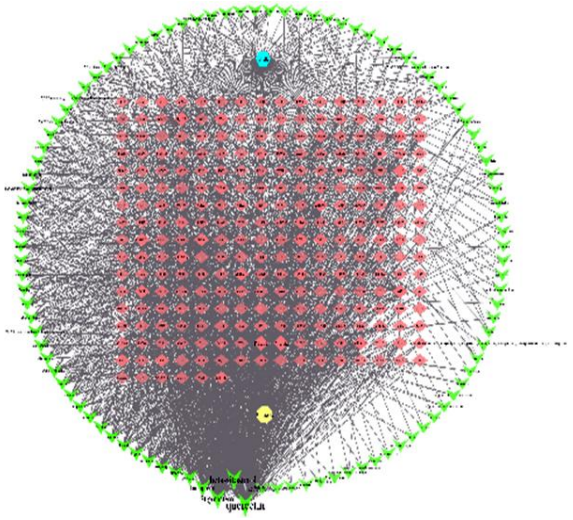

Figure 3. Network of TCM-component-target-disease of CLMD treating vertigo with anxiety. Green: compounds. Red: targets. Yellow: disease. Blue: drug.

The common targets of drugs and diseases were introduced into the Metascape platform for GO functional enrichment analysis. The results showed that these genes were engaged in 440 biological processes (BP), 150 molecular functions (MF), and 113 cellular components (CC). The 10 paths with the highest *P* values for each part were selected (Figure 4). The BP of top 10 paths mainly included cellular responses to organic cyclic compound, inorganic substance, nitrogen compound, and xenobiotic stimulus, *etc*. The top MF mainly included kinase binding, signaling receptor regulator activity, protein homodimerization activity, protein domain specific binding, and heme binding, *etc*. The

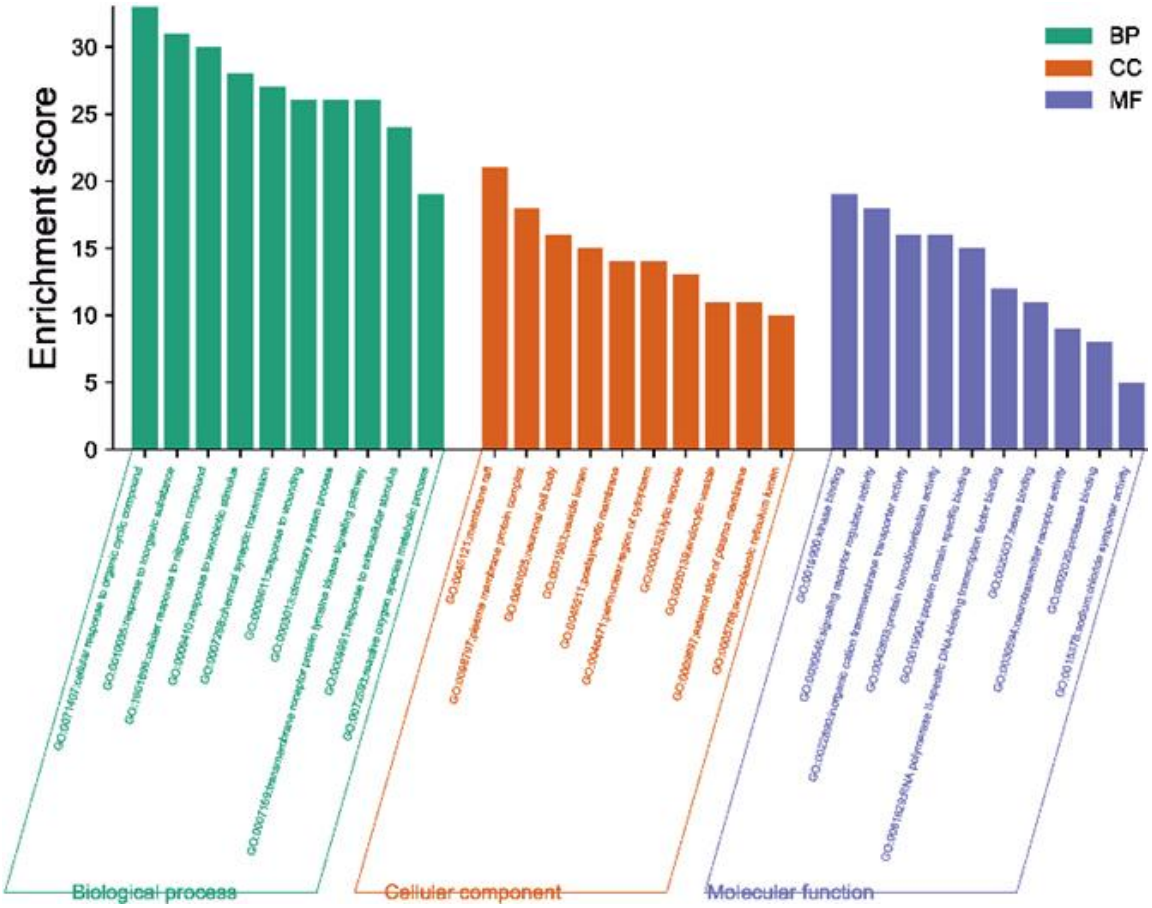

Figure 4. GO functional enrichment analysis.

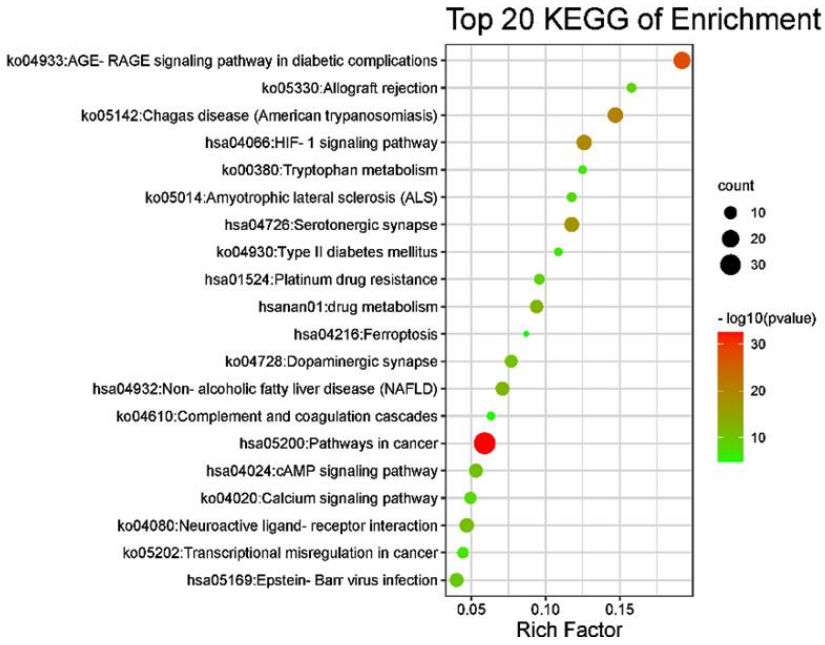

Figure 5. KEGG pathway enrichment analysis.

Table 3. Core targets of CLMD for treating vertigo with anxiety disorder.

Ligand molecules	Core targets		
	***CASP3* (mol)**	***VEGFA* (mol)**	***STAT3* (mol)**
quercetin	-7.6（A）	-7.5（B）	-7.3（C）
baicalein	-7.5（D）	-7.3（E）	-7.5（F）
kaempferol	-7.7（G）	-7.6（H）	-7.4（I）

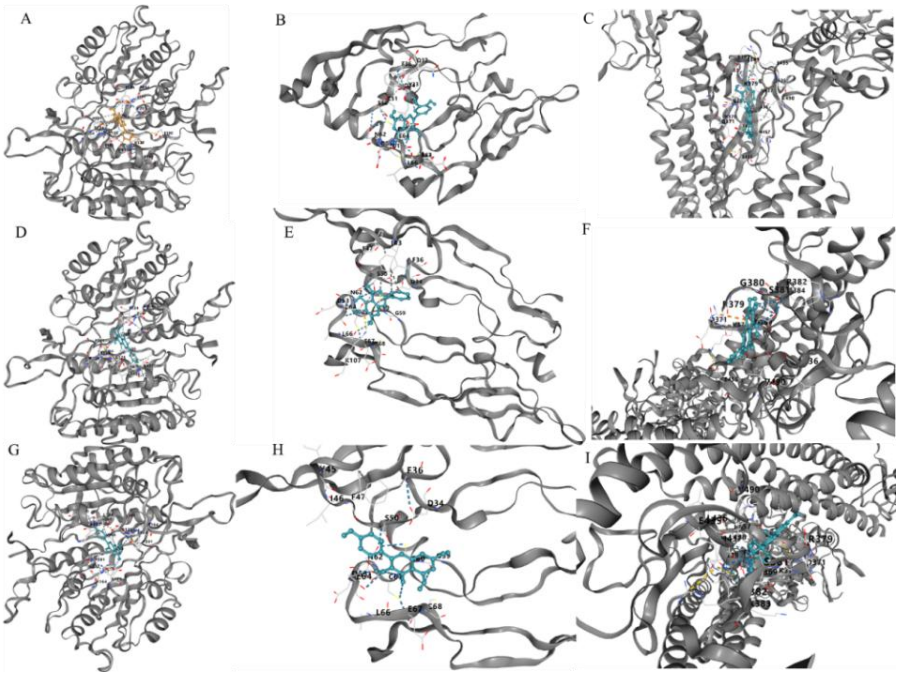

Figure 6. The docking outcomes between the primary target and the active component visualized utilizing PyMol software.

enriched CC evolved dendrite, membrane raft, plasma membrane protein complex, neuronal cell body vesicle lumen, distal axon, and lytic vacuole, *etc*.

KEGG pathway enrichment analysis

A total of 312 KEGG pathways were identified from the Metascape platform. The first 20 pathways were visualized in Figure 5. The KEGG analysis mainly evolved AGE-RAGE signaling pathway in diabetic complications, serotonergic synapse, dopaminergic synapse, cAMP signaling pathway, calcium signaling pathway, *etc*.

Molecular docking

The compounds exhibiting elevated degree values of quercetin, baicalein, and kaempferol in CLMD were subjected to molecular docking analysis with core targets *CASP3*, *VEGFA*, and *STAT3*, respectively. The molecular docking results were shown in Table 3. Binding energy indicated that the two could bind freely. The lower the binding capacity is, the stronger the affinity between receptor and ligand is, and the possibility of interaction between the two is high. The docking outcomes between the primary target and the active component were visualized utilizing Pymol software (Figure 6).

Discussion

Vertigo with anxiety is one of the most common complaints of clinical patients. At present,

conventional Western medicine treatment uses selective serotonin reuptake inhibitors, which exerts side effects such as nausea, ataxia, and even an increased risk of anxiety and depression [8, 9]. Therefore, it is difficult to achieve satisfactory treatment effects, leading to poor compliance. CLMD is one of the classic TCM formulas for treating vertigo with anxiety. However, the mechanism and target of CLMD in the treatment of vertigo with anxiety have not been clarified, which cannot provide sufficient theoretical support for clinical research and application. This study investigated the mechanism by which CLMD might alleviate vertigo with anxiety disorder based on network pharmacology. A total of 100 active ingredients of CLMD were collected through databases including quercetin, beta-sitosterol, stigmasterol, baicalein, and other key active ingredients. Quercetin has against oxidative stress and neuroinflammation, which is the possible therapeutic choice for neurological disorder [10]. Previous study showed that quercetin could improve HPA axis dysregulation and lower the expression of corticosterone and adrenocorticotropic hormones to achieve therapeutic effect against anxiety disorders [11]. Meanwhile, quercetin could inhibit the apoptosis of nerve cells and play a neuroprotective role, and then improve brain blood flow, reduce the vertigo symptoms [12]. Baicalein, a flavonoid, has shown promising results in treating anxiety [13]. Many studies showed that baicalein improved anxiety by regulating GABA receptor [14, 15]. Kaempferol can regulate the levels of NO and NOS and protect endothelial cells from oxidative damage, playing a role in treating vertigo and headache [16].

PPI network analysis suggested that CLMD exerted therapeutic effects on vertigo with anxiety disorder by regulating 101 targets such as *AKT1*, *IL6*, *TNF*, *VEGFA*, and *CASP3*. KEGG enrichment analysis suggested that mechanism of CLMD for vertigo with anxiety treatment was closely correlated with serotonergic synapse, dopaminergic synapse, cAMP signaling pathway, and calcium signaling pathway. Among them, serotonergic synapse and dopaminergic synapse were directly related to vertigo with anxiety. Prior research has indicated that the coexistence of vertigo and anxiety can be attributed to the existence of neural connections between the vestibular nucleus and the nucleus associated with emotions. These connections facilitate interaction between the two nuclei, mediated by neurotransmitters such as serotonin (5-HT) and dopamine (DA) [17-19]. The molecular docking results showed that *CASP3*, *VEGFA*, *STAT3* were the core targets in CLMD. Among them, *CASP3* is involved in the mechanism of apoptosis [20]. Regulating the expression of *CASP3* in vestibular nucleus can effectively improve the vestibular blood supply and alleviate vertigo symptoms [21]. Past studies showed that anxiety disorder was positively correlated with *VEGFA*, which reduced oxidative stress and inflammatory processes by regulating the TLR4/Myd8/NF-β signaling pathway, thus improving anxiety [22, 23]. Those targets could be well attached to the protein, indicating that the target of CLMD was highly related to the disease gene.

This study verified the multi-pathways and multi-targets mechanism of CLMD in the treatment of vertigo with anxiety through the combination of network pharmacology and molecular docking. The results suggested that CLMD might regulate serotonergic synapse and dopaminergic synapse pathways by acting on key targets such as *VEGFA*, *CASP3*, and *STAT3* through quercetin, kaempferol, and baicalein, thereby improving symptoms of vertigo and anxiety. These findings provided novel insight into the mechanism of the action of CLMD on vertigo with anxiety disorder.

Acknowledgements

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