To Explore the Network Pharmacology and Molecular Docking Mechanism of Chaihu Shugan Powder with the “Same Treatment for Different Diseases” for Insomnia and Depression Based on the COVID-19 Pandemic

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Abstract

Background: The classic prescription Chaihu Shugan Powder (CHSGP) has been widely used in clinical Chinese medicine treatment and has clear clinical effects in the treatment of emotional diseases. Based on the increasing incidence of emotional diseases such as insomnia and depression in the population during the COVID-19 pandemic, we will explore the mechanism of CHSGP in the treatment of insomnia and depression with “Same Treatment for Different Diseases”.

Methods: Using a bioinformatics and network pharmacology platform, protein database and STRING database, we collected CHSGP chemical composition and related target data and constructed a “component-target” action network through Gene Ontology and Kyoto Encyclopedia of Genes and Genome pathway enrichment analysis. Molecular docking technology was used to verify key active ingredients and core targets.

Results: A total of 119 active compounds of CHSGP were screened, such as quercetin, kaempferol, and β -sitosterol, and 113 common related targets overlapped with insomnia and depression. GO enrichment and KEGG pathway analysis mainly involved immune, inflammation, cell proliferation, apoptosis, endocrine and other related targets and signaling pathways. Molecular docking showed that small molecular compounds (kaempferol, luteolin, quercetin, 7-methoxy-2-methyl isoflavone and beta-sitosterol) had good binding effects with five target proteins (AKT1, IL1B, IL-6, FOS, GSK3B) to play a role in regulating immunity, the inflammatory response, cell proliferation, apoptosis, and endocrine signaling.

Conclusions: Under the context of the COVID-19 pandemic, it revealed the complex mechanism of multicomponent, multitarget, and multipathway of the classic CHSGP for insomnia and depression, laying a theoretical foundation for its clinical application of its “same treatment for different diseases”.

Highlights

- Network pharmacology and molecular docking were used to explore the mechanism of CHSGP for insomnia and depression with “Same Treatment for Different Diseases”.
- Among the core targets of CHSGP against AKT1, IL1B, IL-6, FOS, and GSK3B in insomnia and depression.
- The AGE-RAGE pathway, neuroactive ligand–receptor interaction, and IL-17 signaling pathway were significantly enriched based on KEGG pathway enrichment analysis.
- The compounds kaempferol, luteolin and quercetin matched well with the target proteins AKT1, IL1B, IL-6, FOS and GSK3B.

1. Introduction

During the global pandemic of COVID-19, economic data in various countries fell, and unemployment rates rose. During the epidemic, many people need to be isolated at home and face outstanding problems, such as work restrictions, academic delays and financial burdens [1]. Many surveys [2–5] have shown that medical staff are at the front line of the fight against the epidemic and under high-intensity work pressure, and they are more likely to suffer from diseases such as depression and sleep disorders. Insomnia, as a common subjective sleep disorder, is mainly manifested as having difficulty falling asleep, sleep maintenance disorder, continuous early awakening, decreased sleep quality, and total sleep time reduction, accompanied by daytime dysfunction [6]. Meanwhile, depression, as a widespread psychological disorder, is characterized by significant and lasting depression, reduced mobility, delayed thinking and cognitive functions with boring, helpless, incompetent, powerless, hopeless and worthless feelings, affecting up to 20% of the global population [7]. Studies have found that the relationship between sleep and depression is two-way, complex and obvious [8]. With the continuous development of the social economy, the prevalence and comorbidities of insomnia and depression are becoming increasingly common [9], and they often occur at the same time [10]. In particular, depression and insomnia caused by the impact of the COVID-19 epidemic have become increasingly prominent, and timely treatment cannot be waited for them [11]. Due to various adverse reactions in the clinical use of Western medicine, many studies have shown that the use of complementary and alternative medicine (CAM) in mental illnesses such as insomnia and depression is a common phenomenon [12]. In addition, compared with pure Western medicine treatment, TCM alone or in combination with Western medicine has the characteristics of quick onset, high cure rate, and fewer side effects [13].

For thousands of years, TCM and its compounds have been used to treat mental illnesses such as insomnia and depression [14]. The earliest record of CHSGP was found in “Jingyue Quanshu” and described it as a classic TCM prescription developed from Sini Soup. Its main components include Chaihu, Baishao, Chuanxiong, Chenpi, Xiangfu, Zhike, and Gancao. The principal active ingredients of CHSGP are monoterpene glycosides, glucose gallic acid, phenolic compounds, lactones, flavonoids and triterpene saponins [15]. CHSGP has the effects of soothing the liver, promoting qi, activating blood and relieving pain and is often used to treat depression, insomnia, anxiety, chronic gastritis, hepatitis and other diseases [16]. As the name suggests, “Same Treatment for Different Diseases” means different diseases can be treated the same. The theory of TCM classifies insomnia and depression into the categories of “insomnia” and “stagnation syndrome”, respectively. The classification often involves multiple organs, such as the liver, spleen, lung, and heart, and can often be treated for liver depression and qi stagnation. This is the fundamental principle of treatment in the “Same Treatment for Different Diseases” of CHSGP. CHSGP matches the menstrual flow of insomnia and depression and can better exert its therapeutic effect. Pharmacological studies have found that the antidepressant pharmacological properties of CHSGP also have a certain

therapeutic effect on insomnia and mainly regulate the neuroendocrine immune network, exerting anti-inflammatory and antioxidative stress effects [17].

Due to its multicomponent and multitarget characteristics, TCM makes in-depth research difficult. Network pharmacology explores the material basis of TCM treatment of diseases from a systemic and holistic perspective by constructing a "drug-target-gene-disease" network and molecular mechanism [18]. This finding is consistent with the overall concept of TCM and Same Treatment for Different Diseases. It provides new ideas, new methods and new ways for TCM mining and analysis and shows the visualization and relevance of data. Its fast and accurate data mining classification and positioning method has been widely recognized [19, 20].

Therefore, this study constructed a "component-target-pathway-disease" association network of CHSGP for insomnia and depression with "Same Treatment for Different Diseases" through network pharmacology and molecular docking. The mechanism of action of multiple targets and pathways provides a certain theoretical basis for clinical applications in treating insomnia-depression during the COVID-19 pandemic.

2. Materials And Methods

2.1. Research ideas

Under the context of the COVID-19 pandemic, this study was based on network pharmacology and molecular docking to explore the research ideas in the mechanism of CHSGP "treating different diseases with the same treatment" insomnia and depression. The experimental flow is shown in Fig. 1.

2.2. Screening the effective ingredients and targets of CHSGP

Through the TCMSP database [21] (<https://tcmospw.com/tcmosp.php>), the pharmacological analysis platform of the Chinese medicine system, OB $\geq$ 30%, DL $\geq$ 0.18, was used as the ingredient screening criteria to search for Chaihu, Baishao, Chuanxiong, Chenpi, Xiangfu, Zhike, and Gancao. The components of the included compounds were predicted and extracted through the TCMSP database. All targets were corrected by the UniProt database [22] (<https://www.uniprot.org/>), and nonhuman targets were removed to obtain "official genes symbol" of all targets. According to the theory of TCM, the effective active ingredient targets of TCM have the characteristics of selective distribution in the body, which is basically consistent with the visceral relationship of the corresponding meridian homing. A Venn diagram was used to show the intersection of the meridian targets of TCM.

2.3. Construction and analysis of the protein interaction network (PPI)

We inputted the common targets of drugs and diseases into the String database [23] (<https://string-db.org/cgi/input.pl>), used the multiple proteins function of the database to construct a PPI network, and set the biological species as "Homo sapiens" at the same time. Finally, a combined score > 0.4 was used as the screening standard to obtain the PPI network model of the intersection target.

2.4 Topological analysis and cluster analysis

In this study, the screened PPI network information was imported into Cytoscape 3.8.0 for network topology analysis, and common key targets were screened based on the degree value and betweenness centrality. We imported the constructed PPI network into Cytoscape 3.8.0, analyzed gene clusters and screened core genes through MCODE module analysis [24].

2.5. Heatmaps of key target genes expressed in organs and tissues

We inputted the key target genes selected by topological analysis into the BioGPS database (<http://biogps.org/#goto=welcome>) and set "current layout" as the "default layout", downloaded the organ and tissue expression data corresponding to the first 20 key target genes. We standardized and visualized the data and plotted the expression heatmaps of the top 20 key target genes in major organs and tissues.

2.6. Visualization of the component-disease-target network and screening of key TCM components

To better understand the complex interactions between components, diseases and corresponding targets, we built a component-disease-target network diagram based on the included components, disease treatments, and targets and introduced Cytoscape 3.8.0 and drew a visual network diagram. We imported the component-disease-target network diagram into Cytoscape 3.8.0 for topological analysis and sorted the components by degree. The higher the degree value, the more important the component (we selected the component greater than the average degree value as the key component for subsequent follow-up research).

2.7. GO enrichment analysis and KEGG pathways analysis

The common targets of drugs and diseases were analyzed for GO enrichment and KEGG pathway analysis. GO enrichment included biological process (BP), molecular function (MF), and cell component (CC) enrichment. Quoting the String database and filtering the items with the corrected P

value < 0.05. At the same time, R 4.0.3 software was used to install and reference clusterProfiler, enrichplot, and ggplot2 packages and draw histograms and bubble charts. We used the Sangerbox tool to visually analyze the drug-disease KEGG signaling pathway and draw a chord diagram.

2.8. Composition-disease-Pathway-Target Network Construction

We imported the component-disease-pathway-target network file into Cytoscape 3.8.0 to draw the path network diagram, which more intuitively showed the characteristics of the multicomponent-multitarget effect of the TCM active ingredients in the treatment of diseases.

2.9. Molecular docking verification

We imported the constructed component-disease-target network diagram to screen the key component compounds, such as kaempferol, luteolin, quercetin, beta-sitosterol, and 7-methoxy-2-methyl isoflavone, into the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>), queried the MOL2 format, and imported Schrodinger software to establish a database, which was prepared as a ligand molecular database for molecular docking [25]. We downloaded the target protein crystal structure from the protein database (<https://www.rcsb.org/>), processed it with the Maestro11.9 platform, processed the protein with Schrodinger's Protein Preparation Wizard [26], and prepared the protein receptor [27]. All compounds were prepared according to the default settings of the LigPre module [28]. Finally, molecular docking and screening were carried out by the SP method, and Pymol2.1 was used for visual analysis.

3. Results

3.1. Inquiry and analysis of TCM ingredients and target information

Using the TCMSP database and setting $OB \geq 30\%$ and $DL \geq 0.18$ as the screening conditions, the components of the included compounds were predicted by the TCMSP database. All targets were calibrated by the UniProt database, and nonhuman targets were removed. After summarizing and deleting the duplicates, we got 17 compound components and 179 targets of Chaihu, 13 compound components and 86 targets of Baishao, 5 compound components and 65 targets of Chenpi, 7 compound components and 30 targets of Chuanxiong, Gancao has 93 compound components and 216 targets, Xiangfu has 18 compound components and 210 targets, Zhike has 5 compound components and 88 targets. The analysis of Guijing in CHSGP showed that Chaihu, Baishao, Chuanxiong, and Xiangfu belonged to the liver channel with 18 common targets; Baishao, Xiangfu, Zhike, Chenpi, and Gancao belonged to the spleen channel with 27 common targets; Chaihu, Chenpi, and Gancao belonged to the lung channel with 39 common targets, as shown in Table 1. The above data showed that each Chinese medicine of CHSGS mainly belonged to the liver, spleen, and lung meridians, which were also in line with the location and pathogenesis of insomnia and depression and reflected the connotation of "Same Treatment for Different Diseases", as shown in Fig. 2.

Table 1
Basic information of active ingredients of CHSGS

Mol ID	Molecule Name	OB (%)	DL	Source	Mol ID	Molecule Name	OB (%)	DL	Source
MOL001645	Linoleyl acetate	42.10	0.20	ChaiHu	MOL004990	7,2',4'-trihydroxy-5-methoxy-3-aryl coumarin	83.71	0.27	Gan Cao
MOL002776	Baicalin	40.12	0.75		MOL004989	6-prenylated eriodictyol	39.22	0.41	
MOL000449	Stigmasterol	43.83	0.76		MOL004988	Kanzonol F	32.47	0.89	
MOL000354	isorhamnetin	49.60	0.31		MOL004985	icos-5-enoic acid	30.70	0.20	
MOL000422	kaempferol	41.88	0.24		MOL004980	Inflacoumarin A	39.71	0.33	
MOL004598	3,5,6,7-tetramethoxy-2-(3,4,5-trimethoxyphenyl)chromone	31.97	0.59		MOL004978	2-[(3R)-8,8-dimethyl-3,4-dihydro-2H-pyrano[6,5-f]chromen-3-yl]-5-methoxyphenol	36.21	0.52	
MOL004609	Areapillin	48.96	0.41		MOL004974	3'-Methoxyglabridin	46.16	0.57	
MOL013187	Cubebin	57.13	0.64		MOL004966	3'-Hydroxy-4'-O-Methylglabridin	43.71	0.57	
MOL004624	Longikaurin A	47.72	0.53		MOL004961	Quercetin der.	46.45	0.33	
MOL004628	Octalupine	47.82	0.28		MOL004959	1-Methoxyphaseollidin	69.98	0.64	
MOL004644	Sainfuran	79.91	0.23		MOL004957	HMO	38.37	0.21	
MOL004648	Troxerutin	31.60	0.28		MOL004949	Isolicoflavonol	45.17	0.42	
MOL004653	(+)-Anomalin	46.06	0.66		MOL004948	Isoglycyrol	44.70	0.84	
MOL004702	saikosaponin c _{qt}	30.50	0.63		MOL004945	(2S)-7-hydroxy-2-(4-hydroxyphenyl)-8-(3-methylbut-2-enyl)chroman-4-one	36.57	0.32	
MOL004718	α-spinasterol	42.98	0.76	ChenPi	MOL004941	(2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one	71.12	0.18	
MOL000490	petunidin	30.05	0.31		MOL004935	Sigmoidin-B	34.88	0.41	
MOL000098	quercetin	46.43	0.28		MOL004924	(-)-Medicocarpin	40.99	0.95	
MOL000359	sitosterol	36.91	0.75		MOL004917	glycyroside	37.25	0.79	
MOL004328	naringenin	59.29	0.21		MOL004915	Eurycarpin A	43.28	0.37	
MOL005100	5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)chroman-4-one	47.74	0.27		MOL004914	1,3-dihydroxy-8,9-dimethoxy-6-benzofurano[3,2-c]chromenone	62.90	0.53	
MOL005815	Citromitin	86.90	0.51		MOL004913	1,3-dihydroxy-9-methoxy-6-benzofurano[3,2-c]chromenone	48.14	0.43	
MOL005828	nobiletin	61.67	0.52		MOL004912	Glabrone	52.51	0.50	
MOL001910	11α,12α-epoxy-3β-23-dihydroxy-30-norolean-20-en-28,12β-olide	64.77	0.38		MOL004911	Glabrene	46.27	0.44	
MOL001918	paeoniflorgenone	87.59	0.37	BaiShao	MOL004910	Glabranin	52.90	0.31	
MOL001919	(3S,5R,8R,9R,10S,14S)-3,17-dihydroxy-4,4,8,10,14-pentamethyl-2,3,5,6,7,9-hexahydro-1H-cyclopenta[a]phenanthrene-15,16-dione	43.56	0.53		MOL004908	Glabridin	53.25	0.47	
MOL001921	Lactiflorin	49.12	0.80		MOL004907	Glyzaglabrin	61.07	0.35	

Mol ID	Molecule Name	OB (%)	DL	Source	Mol ID	Molecule Name	OB (%)	DL	Source
MOL001924	paeoniflorin	53.87	0.79		MOL004905	3,22-Dihydroxy-11-oxo-delta(12)-oleanene-27-alpha-methoxycarbonyl-29-oic acid	34.32	0.55	
MOL001925	paeoniflorin_qt	68.18	0.40		MOL004904	licopyranocoumarin	80.36	0.65	
MOL001928	albiflorin_qt	66.64	0.33		MOL004903	liquiritin	65.69	0.74	
MOL001930	benzoyl paeoniflorin	31.27	0.75		MOL004898	(E)-3-[3,4-dihydroxy-5-(3-methylbut-2-enyl)phenyl]-1-(2,4-dihydroxyphenyl)prop-2-en-1-one	46.27	0.31	
MOL000211	Mairin	55.38	0.78		MOL004891	shinpterocarpin	80.30	0.73	
MOL000358	beta-sitosterol	36.91	0.75		MOL004885	licoisoflavanone	52.47	0.54	
MOL000359	sitosterol	36.91	0.75		MOL004884	Licoisoflavone B	38.93	0.55	
MOL000422	kaempferol	41.88	0.24		MOL004883	Licoisoflavone	41.61	0.42	
MOL000492	(+)-catechin	54.83	0.24		MOL004882	Licocoumarone	33.21	0.36	
MOL001494	Mandenol	42.00	0.19	Chuan	MOL004879	Glycyrin	52.61	0.47	
MOL002135	Myricanone	40.60	0.51	Xiong	MOL004866	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-(3-methylbut-2-enyl)chromone	44.15	0.41	
MOL002140	Perlolryne	65.95	0.27		MOL004864	5,7-dihydroxy-3-(4-methoxyphenyl)-8-(3-methylbut-2-enyl)chromone	30.49	0.41	
MOL002151	senkyunone	47.66	0.24		MOL004863	3-(3,4-dihydroxyphenyl)-5,7-dihydroxy-8-(3-methylbut-2-enyl)chromone	66.37	0.41	
MOL002157	wallichilide	42.31	0.71		MOL004860	licorice glycoside E	32.89	0.27	
MOL000359	sitosterol	36.91	0.75		MOL004857	Gancaonin B	48.79	0.45	
MOL000433	FA	68.96	0.71		MOL004856	Gancaonin A	51.08	0.4	
MOL003044	Chryseriol	35.85	0.27	Xiang	MOL004855	Licoricone	63.58	0.47	
MOL000354	isorhamnetin	49.60	0.31	Fu	MOL004849	3-(2,4-dihydroxyphenyl)-8-(1,1-dimethylprop-2-enyl)-7-hydroxy-5-methoxy-coumarin	59.62	0.43	
MOL003542	8-Isopentenyl-kaempferol	38.04	0.39		MOL004848	licochalcone G	49.25	0.32	
MOL000358	beta-sitosterol	36.91	0.75		MOL004841	Licochalcone B	76.76	0.19	
MOL000359	sitosterol	36.91	0.75		MOL004838	8-(6-hydroxy-2-benzofuranyl)-2,2-dimethyl-5-chromenol	58.44	0.38	
MOL004027	1,4-Epoxy-16-hydroxyheneicos-1,3,12,14,18-pentaene	45.10	0.24		MOL004835	Glypallichalcone	61.60	0.19	
MOL004053	Isodalbergin	35.45	0.20		MOL004833	Phaseolinisoflavan	32.01	0.45	
MOL004058	Khell	33.19	0.19		MOL004829	Glepidotin B	64.46	0.34	
MOL004059	khellol glucoside	74.96	0.72		MOL004828	Glepidotin A	44.72	0.35	
MOL010489	Resivit	30.84	0.27		MOL004827	Semilicoisoflavone B	48.78	0.55	

Mol ID	Molecule Name	OB (%)	DL	Source	Mol ID	Molecule Name	OB (%)	DL	Source
MOL004068	rosenonolactone	79.84	0.37	ZhiKe	MOL004824	(2S)-6-(2,4-dihydroxyphenyl)-2-(2-hydroxypropan-2-yl)-4-methoxy-2,3-dihydrofuro[3,2-g]chromen-7-one	60.25	0.63	
MOL004071	Hyndarin	73.94	0.64		MOL004820	kanzonols W	50.48	0.52	
MOL004074	stigmasterol glucoside_qt	43.83	0.76		MOL004815	(E)-1-(2,4-dihydroxyphenyl)-3-(2,2-dimethylchromen-6-yl)prop-2-en-1-one	39.62	0.35	
MOL004077	sugeonyl acetate	45.08	0.20		MOL004814	Isotrifoliol	31.94	0.42	
MOL000422	kaempferol	41.88	0.24		MOL004811	Glyasperin C	45.56	0.4	
MOL000449	Stigmasterol	43.83	0.76		MOL004810	glyasperin F	75.84	0.54	
MOL000006	luteolin	36.16	0.25		MOL004808	glyasperin B	65.22	0.44	
MOL000098	quercetin	46.43	0.28		MOL004806	euchrenone	30.29	0.57	
MOL013381	Marmin	38.23	0.31		MOL004805	(2S)-2-[4-hydroxy-3-(3-methylbut-2-enyl)phenyl]-8,8-dimethyl-2,3-dihydropyrano[2,3-f]chromen-4-one	31.79	0.72	
MOL002341	Hesperetin	70.31	0.27		MOL004328	naringenin	59.29	0.21	
MOL000358	beta-sitosterol	36.91	0.75	Gan Cao	MOL003896	7-Methoxy-2-methyl isoflavone	42.56	0.2	
MOL004328	naringenin	59.29	0.21		MOL003656	Lupiwighteone	51.64	0.37	
MOL005828	nobiletin	61.67	0.52		MOL002844	Pinocembrin	64.72	0.18	
MOL005020	dehydroglyasperins C	53.82	0.37		MOL002565	Medicarpin	49.22	0.34	
MOL005018	Xambioona	54.85	0.87		MOL002311	Glycyrol	90.78	0.67	
MOL005017	Phaseol	78.77	0.58		MOL001792	DFV	32.76	0.18	
MOL005016	Odoratin	49.95	0.3		MOL001484	Inermine	75.18	0.54	
MOL005013	18 α -hydroxyglycyrrhetic acid	41.16	0.71		MOL000500	Vestitol	74.66	0.21	
MOL005012	Licoagroisoflavone	57.28	0.49		MOL000497	licochalcone a	40.79	0.29	
MOL005008	Glycyrrhiza flavonol A	41.28	0.6		MOL000422	kaempferol	41.88	0.24	
MOL005007	Glyasperins M	72.67	0.59		MOL000417	Calycosin	47.75	0.24	
MOL005003	Licoagrocarpin	58.81	0.58		MOL000392	formononetin	69.67	0.21	
MOL005001	Gancaonin H	50.10	0.78		MOL000359	sitosterol	36.91	0.75	
MOL005000	Gancaonin G	60.44	0.39		MOL000354	isorhamnetin	49.60	0.31	
MOL004996	gadelaic acid	30.70	0.20		MOL000239	Jaranol	50.83	0.29	
MOL004993	8-prenylated eriodictyol	53.79	0.4		MOL000211	Mairin	55.38	0.78	
MOL004991	7-Acetoxy-2-methylisoflavone	38.92	0.26		MOL000098	quercetin	46.43	0.28	
MOL005020	dehydroglyasperins C	53.82	0.37						

3.2. Disease targets search

We searched human genes through the GeneCards, NCBI and OMIM databases, among which depression obtained 12995 related targets in the GeneCards database, 556 related targets in the NCBI database and 3 related targets in the OMIM database. Insomnia obtained 2589 related targets

in the GeneCards database, 50 related targets in the NCBI database, and 4 related targets in the OMIM database.

3.3 Venn diagram of common targets in drugs and diseases

We inputted the selected drug targets and disease targets into Venn diagram production software (Venny 2.1) and obtained 113 common targets, which were used as common predictive targets for the following pathway enrichment analysis, as shown in Fig. 3.

3.4. Construction and analysis of PPI network

There were 113 nodes, 1365 edges, and an average degree of 24.2 in the network. Figure 4A shows the PPI network diagram exported from the STRING website, and Fig. 4B shows the PPI network diagram drawn by Cytoscape software. The color and size of the nodes in Fig. 4B were adjusted according to the degree value. The larger the color, the redder the color and the greater the degree value. Thickness from thick to thin represents the edge betweenness from large to small.

3.5. Topological analysis and MCODE cluster analysis

3.5.1. Topological analysis

We imported the PPI network into Cytoscape3.8.0 [29], used the Network Analyzer tool to perform topology analysis, and sorted by degree; the greater the degree value, the greater the role of the node in the network graph. We selected genes with scores greater than the average score as key targets. A total of 42 key targets were screened, and the top 20 targets were listed as AKT1, IL6, IL1B, CASP3, MAPK3, PPARG, MMP9, CXCL8, IL10, HSP90AA1, ESR1, FOS, HIFIA, CREB1, NOS3, HMOX1, MMP2, CCND1, ERBB2 and CASP8. We used R 4.0.3 to draw pictures of the first top target points, where the abscissa was the degree value of each target point, as shown in Fig. 5.

3.5.2. MCODE cluster analysis

We imported the constructed PPI network into Cytoscape 3.8.0 and opened the MCODE module [24] to analyze gene clusters and screened core targets to obtain 7 gene clusters and 7 core genes (FOS, GABRA2, GSK3B, PON1, APOB, CYP1B1, ADRA1A). The specific results are shown in Table 2.

Table 2. MCODE cluster analysis information table for the common targets of CHSGP, insomnia and depression

5		5	6	APOB, THBD, F2, PLAT, LDLR
6		3	3	NR1I3, UGT1A1, CYP1B1
7		3	3	ADRA1A, ADRA1D, ADRA1B

3.6. Constructing a composition-disease target network and screening key ingredients

To better understand the complex interactions among ingredients, diseases and corresponding targets, we constructed an “ingredient-disease-target” network based on the included ingredients, the treatment of diseases and the action targets. We screened 119 core components, such as MOL000098 (quercetin), MOL000422 (kaempferol), MOL000358 (β -sitosterol), MOL003896 (7-methoxy-2-methyl isoflavone), and MOL000006 (luteolin), and 113 core targets, such as AKT1, IL6, IL1B, CASP3, and MAPK3. We imported the component-disease-target network into Cytoscape 3.8.0 for topological analysis. The degree was sorted according to the ingredients. The higher the degree, the more important the ingredient, and the results are shown in Table 2. Table 3 shows that the top 5 compounds with a median value of the network were MOL000098 (quercetin), MOL000422 (kaempferol), MOL000358 (β -sitosterol), MOL003896 (7-methoxy-2-methyl) isoflavones), and MOL000006 (luteolin), which could provide small drug compounds for subsequent molecular docking.

Table 3
Information table of CHSGP key ingredients

MOL ID	Name	Average Shortest Path Length	Betweenness Centrality	Closeness Centrality	Degree
MOL000098	quercetin	1.958159	0.116804	0.510684	67
MOL000422	kaempferol	2.242678	0.039975	0.445896	33
MOL000358	beta-sitosterol	2.451883	0.020367	0.40785	26
MOL003896	7-Methoxy-2-methyl isoflavone	2.351464	0.011754	0.425267	23
MOL000006	luteolin	2.460251	0.012164	0.406463	21
MOL004328	naringenin	2.426778	0.023098	0.412069	20
MOL000354	isorhamnetin	2.376569	0.012626	0.420775	19
MOL002565	Medicarpin	2.41841	0.008852	0.413495	19
MOL000449	Stigmasterol	2.711297	0.00895	0.368827	18
MOL004071	Hyndarin	2.543933	0.008647	0.393092	18
MOL000392	formononetin	2.41841	0.004622	0.413495	17
MOL000500	Vestitol	2.451883	0.004071	0.40785	15
MOL004959	1-Methoxyphaseollidin	2.443515	0.002943	0.409247	15
MOL005828	nobiletin	2.460251	0.012514	0.406463	15
MOL000497	licochalcone a	2.460251	0.004353	0.406463	14
MOL004835	Glypallichalcone	2.460251	0.002517	0.406463	14
MOL004891	shinpterocarpin	2.460251	0.003491	0.406463	14
MOL004991	7-Acetoxy-2-methylisoflavone	2.435146	0.003242	0.410653	14
MOL005003	Licoagrocarpin	2.443515	0.002204	0.409247	14
MOL004978	2-[(3R)-8,8-dimethyl-3,4-dihydro-2H-pyrano[6,5-f]chromen-3-yl]-5-methoxyphenol	2.476987	0.001844	0.403716	13
MOL004957	HMO	2.485356	0.001897	0.402357	12
MOL002135	Myricanone	2.476987	0.006864	0.403716	11
MOL004857	Gancaonin B	2.493724	0.001127	0.401007	11
MOL004966	3'-Hydroxy-4'-O-Methylglabridin	2.493724	0.001083	0.401007	11
MOL004974	3'-Methoxyglabridin	2.493724	9.93E-04	0.401007	11
MOL005007	Glyasperins M	2.502092	0.001827	0.399666	11
MOL003542	8-Isopentenyl-kaempferol	2.468619	0.003335	0.405085	10
MOL004808	glyasperin B	2.518828	7.86E-04	0.39701	10
MOL004828	Glepidotin A	2.493724	0.001075	0.401007	10
MOL004833	Phaseolinisoflavan	2.543933	8.73E-04	0.393092	10
MOL004908	Glabridin	2.543933	8.73E-04	0.393092	10
MOL000417	Calycosin	2.51046	5.90E-04	0.398333	9
MOL001484	Inermine	2.518828	0.001288	0.39701	9
MOL002844	Pinocembrin	2.502092	0.001513	0.399666	9
MOL004811	Glyasperin C	2.527197	5.57E-04	0.395695	9
MOL004824	(2S)-6-(2,4-dihydroxyphenyl)-2-(2-hydroxypropan-2-yl)-4-methoxy-2,3-dihydrofuro[3,2-g]chromen-7-one	2.585774	5.66E-04	0.386731	9

MOL ID	Name	Average Shortest Path Length	Betweenness Centrality	Closeness Centrality	Degree
MOL004841	Licochalcone B	2.51046	5.90E-04	0.398333	9
MOL004849	3-(2,4-dihydroxyphenyl)-8-(1,1-dimethylprop-2-enyl)-7-hydroxy-5-methoxy-coumarin	2.527197	6.08E-04	0.395695	9
MOL004856	Gancaonin A	2.527197	5.57E-04	0.395695	9
MOL004885	licoisoflavanone	2.518828	5.43E-04	0.39701	9
MOL004907	Glyzaglabrin	2.518828	6.37E-04	0.39701	9
MOL004911	Glabrene	2.51046	5.90E-04	0.398333	9
MOL004912	Glabrone	2.51046	6.39E-04	0.398333	9
MOL004941	(2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one	2.502092	0.001513	0.399666	9
MOL005000	Gancaonin G	2.527197	6.58E-04	0.395695	9
MOL001792	DFV	2.527197	9.10E-04	0.395695	8
MOL003044	Chryseriol	2.527197	0.001336	0.395695	8
MOL003656	Lupiwighteone	2.535565	3.99E-04	0.394389	8
MOL004053	Isodalbergin	2.535565	0.001437	0.394389	8
MOL004810	glyasperin F	2.527197	3.69E-04	0.395695	8
MOL004815	(E)-1-(2,4-dihydroxyphenyl)-3-(2,2-dimethylchromen-6-yl)prop-2-en-1-one	2.535565	4.09E-04	0.394389	8
MOL004827	Semilicoisoflavone B	2.535565	4.73E-04	0.394389	8
MOL004848	licochalcone G	2.552301	3.64E-04	0.391803	8
MOL004884	Licoisoflavone B	2.594142	3.79E-04	0.385484	8
MOL004915	Eurycarpin A	2.535565	3.99E-04	0.394389	8
MOL004945	(2S)-7-hydroxy-2-(4-hydroxyphenyl)-8-(3-methylbut-2-enyl)chroman-4-one	2.527197	5.67E-04	0.395695	8
MOL004961	Quercetin der.	2.527197	3.69E-04	0.395695	8
MOL004990	7,2',4'-trihydroxy-5-methoxy-3-aryl coumarin	2.527197	3.69E-04	0.395695	8
MOL005016	Odoratin	2.527197	3.69E-04	0.395695	8
MOL002311	Glycyrol	2.60251	3.46E-04	0.384244	7
MOL004814	Isotrifoliol	2.560669	3.60E-04	0.390523	7
MOL004820	kanzonols W	2.543933	2.55E-04	0.393092	7
MOL004863	3-(3,4-dihydroxyphenyl)-5,7-dihydroxy-8-(3-methylbut-2-enyl)chromone	2.543933	3.29E-04	0.393092	7
MOL004864	5,7-dihydroxy-3-(4-methoxyphenyl)-8-(3-methylbut-2-enyl)chromone	2.560669	1.78E-04	0.390523	7
MOL004879	Glycyrin	2.60251	3.49E-04	0.384244	7
MOL004883	Licoisoflavone	2.543933	4.31E-04	0.393092	7
MOL004904	licopyranocoumarin	2.60251	3.93E-04	0.384244	7
MOL004949	Isolicoflavanol	2.543933	3.29E-04	0.393092	7
MOL004980	Inflacoumarin A	2.51046	5.69E-04	0.398333	7
MOL005008	Glycyrrhiza flavonol A	2.560669	2.68E-04	0.390523	7
MOL005012	Licoagrisoflavone	2.60251	2.55E-04	0.384244	7
MOL005017	Phaseol	2.543933	4.31E-04	0.393092	7
MOL005020	dehydroglyasperins C	2.552301	3.07E-04	0.391803	7

MOL ID	Name	Average Shortest Path Length	Betweenness Centrality	Closeness Centrality	Degree
MOL000359	sitosterol	2.527197	0.005143	0.395695	6
MOL000490	petunidin	2.543933	0.001124	0.393092	6
MOL004805	(2S)-2-[4-hydroxy-3-(3-methylbut-2-enyl)phenyl]-8,8-dimethyl-2,3-dihydropyrano[2,3-f]chromen-4-one	2.635983	8.38E-05	0.379365	6
MOL004829	Glepidotin B	2.552301	4.00E-04	0.391803	6
MOL004855	Licoricone	2.610879	2.78E-04	0.383013	6
MOL004910	Glabranin	2.552301	3.65E-04	0.391803	6
MOL004913	1,3-dihydroxy-9-methoxy-6-benzofurano[3,2-c]chromenone	2.569038	1.41E-04	0.389251	6
MOL000239	Jaranol	2.560669	1.84E-04	0.390523	5
MOL004077	sugeonyl acetate	3.263598	4.74E-04	0.30641	5
MOL004598	3,5,6,7-tetramethoxy-2-(3,4,5-trimethoxyphenyl)chromone	2.619247	7.81E-04	0.381789	5
MOL004609	Areapillin	2.552301	8.83E-04	0.391803	5
MOL004624	Longikaurin A	3.230126	5.23E-04	0.309585	5
MOL004806	euchrenone	2.661088	0.001185	0.375786	5
MOL004838	8-(6-hydroxy-2-benzofuranyl)-2,2-dimethyl-5-chromenol	2.585774	2.14E-04	0.386731	5
MOL004866	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-(3-methylbut-2-enyl)chromone	2.543933	2.88E-04	0.393092	5
MOL004882	Licocoumarone	2.577406	1.09E-04	0.387987	5
MOL004898	(E)-3-[3,4-dihydroxy-5-(3-methylbut-2-enyl)phenyl]-1-(2,4-dihydroxyphenyl)prop-2-en-1-one	2.577406	1.00E-04	0.387987	5
MOL004914	1,3-dihydroxy-8,9-dimethoxy-6-benzofurano[3,2-c]chromenone	2.577406	1.00E-04	0.387987	5
MOL000492	(+)-catechin	2.560669	0.001843	0.390523	4
MOL002341	Hesperetin	2.711297	6.85E-04	0.368827	4
MOL004058	Khell	2.594142	5.80E-04	0.385484	4
MOL004935	Sigmoidin-B	2.594142	1.39E-04	0.385484	4
MOL004948	Isoglycyrol	2.661088	3.77E-05	0.375786	4
MOL004989	6-prenylated eriodictyol	2.594142	6.51E-05	0.385484	4
MOL005001	Gancaonin H	2.594142	1.39E-04	0.385484	4
MOL005018	Xambioona	2.669456	3.34E-05	0.374608	4
MOL005100	5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)chroman-4-one	2.711297	9.02E-04	0.368827	4
MOL013187	Cubebin	2.661088	5.88E-04	0.375786	4
MOL000433	FA	2.820084	9.38E-04	0.354599	3
MOL001924	paeoniflorin	3.39749	2.70E-04	0.294335	3
MOL002157	wallichilide	3.39749	5.56E-04	0.294335	3
MOL004903	liquiritin	2.736402	3.02E-04	0.365443	3
MOL004988	Kanzonol F	2.686192	1.86E-05	0.372274	3
MOL004993	8-prenylated eriodictyol	2.60251	4.00E-05	0.384244	3
MOL010489	Resivit	2.702929	2.67E-04	0.369969	3
MOL001494	Mandenol	2.962343	6.90E-04	0.337571	2
MOL001645	Linoleyl acetate	2.953975	1.51E-04	0.338527	2

MOL ID	Name	Average Shortest Path Length	Betweenness Centrality	Closeness Centrality	Degree
MOL001918	paeoniflorgenone	3.330544	1.14E-04	0.300251	2
MOL001919	(3S,5R,8R,9R,10S,14S)-3,17-dihydroxy-4,4,8,10,14-pentamethyl-2,3,5,6,7,9-hexahydro-1H-cyclopenta[a]phenanthrene-15,16-dione	3.389121	1.35E-04	0.295062	2
MOL002140	Perlolirine	3.112971	4.34E-04	0.321237	2
MOL004068	rosenonolactone	3.330544	1.00E-04	0.300251	2
MOL004653	(+)-Anomalin	3.087866	1.27E-04	0.323848	2
MOL004718	α -spinasterol	3.355649	1.74E-04	0.298005	2
MOL004924	(-)-Medicocarpin	2.753138	2.33E-05	0.363222	2
MOL005815	Citromitin	2.803347	3.50E-04	0.356716	2
MOL013381	Marmin	3.154812	1.47E-04	0.316976	2

3.7. Enrichment analysis of GO and KEGG pathway

We enriched the BP, MF, CC of GO analysis and KEGG pathway enrichment on the common drug-disease targets. By citing the String database, the items with the corrected $P < 0.05$ were screened, and a total of 1850 biological processes were enriched, which included reactions to drugs, reactions to metal ions, reactions to lipopolysaccharides, reactions to bacteria-derived molecules, tube diameter adjustment, blood vessel diameter adjustment, tube diameter adjustment, vascular processes in the circulatory system, response to alcohol, cell response to chemical stress, response to oxidative stress, and so on. They involved 155 molecular functions related to membrane rafts, membrane microzones, membrane regions, postsynaptic membranes, components of postsynaptic membranes, internal components of postsynaptic membranes, synaptic membranes, components of synaptic membranes, internal components of synaptic membranes, presynaptic membrane membrane membrane components, etc. They related 74 cell components, such as neurotransmitter receptor activity, postsynaptic neurotransmitter receptor activity, G protein-coupled amine receptor activity, catecholamine binding, drug binding, and participation in postsynaptic regulation. Neurotransmitter receptor activity of membrane potential, nuclear receptor activity, ligand-activated transcription factor activity, emitter-gated ion channel activity, emitter-gated channel activity, etc. Excluding tuberculosis, whooping cough, malaria, and measles, we enriched 149 signaling pathways, which mainly included lipids and atherosclerosis, AGE-RAGE signaling pathway in diabetic complications, fluid shear stress and atherosclerosis, Kaposi's sarcoma-associated herpes virus infection, neuroactive ligand-receptor interaction, IL-17 signaling pathway, Chagas disease, TNF signaling pathway, toxoplasmosis, endocrine resistance, chemical carcinogenesis-receptor activation, Th17 cell differentiation, dopaminergic synapses, hepatitis B, Toll-like receptor signaling pathway, osteoclast differentiation, nonalcoholic fatty liver and other signaling pathways related to inflammation, immunity, and oxidative stress. After installing and citing the clusterProfiler package of R 4.0.3, we drew a histogram and bubble chart to visualize the top 20 items with the highest saliency, as shown in Fig. 6A, 6B, 6C and 6D.

3.8. Construction component-disease-pathway-target network and chord diagram visualization

We imported the component-disease-pathway-target network file into Cytoscape 3.8.0 to draw the path network diagram. More intuitively, the characteristics of the multicomponent-multitarget effect of the TCM active ingredients in the treatment of diseases were revealed, as shown in Fig. 7 (blue is the compound, yellow is the target of the Chinese medicine on the disease, green is the top 20 most significant pathways, red is the disease that is the disease, and purple is the Chinese medicine). The KEGG signaling pathway of drug-disease was visually analyzed using the Sangerbox tool, and it was found that the top 20 signaling pathways significantly enriched by KEGG involved 85 genes, as shown in Fig. 8.

3.10. Molecular docking

We used Pymol2.1 software to visualize the complex formed by the compounds and proteins after molecular docking (select the compound with the most negative binding energy score for each target), which obtained the binding mode of the compound and the protein, as shown in Table 4. According to the binding mode, the amino acid residues where the compound binds to the protein pocket could be clearly seen; for example, kaempferol binds to AKT1. The active amino acid residues included VAL-164, GLU-228, ALA-230, ASP-292, MET-281, GLU-234, etc. Kaempferol is a flavonoid compound that contains multiple hydroxyl groups and can interact with the active groups of amino acids to form hydrogen bonds. For example, it could interact with the active groups of GLU-228, ASP-292, ALA-230, and GLU-234. The strong hydrogen bond interaction, with an average hydrogen bond distance of 2.0 Å, was much smaller than the traditional hydrogen bond of 3.5 Å, which played an important role in stabilizing small molecule ligands. In summary, kaempferol, luteolin, quercetin, and 7-methoxy-2-methyl isoflavone compounds matched well with the five target protein targets, could form stable complexes, and had a good relationship with the protein, which also indirectly verified these compounds. It had a regulatory effect on AKT1, IL1B, IL-6, FOS, GSK3B, GABRA and other targets. When the binding energy is less than 0, it is

considered that the ligand and receptor can bind freely, and the lower the binding energy is, the stronger the affinity. These results indicated that the molecular docking results were consistent with the screening results of network pharmacology, which preliminarily verified the reliability of network pharmacology, as shown in Fig. 9.

Table 4. The molecular docking results of selected compounds

Target	Compounds	Structure	Docking Score (kcal/mol)	Combination Type
AKT1	Quercetin		-7.81	Hydrogen bonds, Hydrophobic interactive, π-stacking
AKT1	Luteolin		-7.18	Hydrogen bonds, Hydrophobic interactive, π-stacking
AKT1	Kaempferol		-7.72	Hydrogen bonds, Hydrophobic interactive
AKT1	7-Methoxy-2-methyl-isoflavone		-6.79	Hydrogen bonds, Hydrophobic interactive, π-stacking
AKT1	beta-Sitosterol		-5.90	Hydrophobic interactive
GSK3B	Quercetin		-7.39	Hydrogen bonds, Hydrophobic interactive
GSK3B	Luteolin		-8.23	Hydrogen bonds, Hydrophobic interactive, π-stacking
GSK3B	Kaempferol		-7.85	Hydrogen bonds, Hydrophobic interactive, π-stacking
GSK3B	7-Methoxy-2-methyl-isoflavone		-7.28	Hydrogen bonds, Hydrophobic interactive
GSK3B	beta-Sitosterol		-5.96	Hydrogen bonds, Hydrophobic interactive
IL1B	Quercetin		-6.96	Hydrogen bonds, Hydrophobic interactive, π-stacking
IL1B	Luteolin		-6.43	Hydrogen bonds, Hydrophobic interactive
IL1B	Kaempferol		-6.47	Hydrogen bonds, Hydrophobic interactive
IL1B	7-Methoxy-2-methyl-isoflavone		-6.48	Hydrogen bonds, Hydrophobic interactive, π-stacking
IL1B	beta-Sitosterol		-5.63	Hydrogen bonds, Hydrophobic interactive
IL6	Quercetin		-6.68	Hydrogen bonds, Hydrophobic interactive, π-stacking
IL6	Luteolin		-6.24	Hydrogen bonds, Hydrophobic interactive, π-stacking
IL6	Kaempferol		-6.73	Hydrogen bonds, Hydrophobic interactive, π-stacking
IL6	7-Methoxy-2-methyl-isoflavone		-6.12	Hydrogen bonds, Hydrophobic interactive, π-stacking
IL6	beta-Sitosterol		-5.34	Hydrogen bonds, Hydrophobic interactive
GABRA2	Quercetin		-6.71	Hydrogen bonds, Hydrophobic interactive, π-stacking
GABRA2	Luteolin		-6.58	Hydrogen bonds, Hydrophobic interactive, π-stacking
GABRA2	Kaempferol		-6.62	Hydrogen bonds, Hydrophobic interactive, π-stacking
GABRA2	7-Methoxy-2-methyl-isoflavone		-6.19	Hydrogen bonds, Hydrophobic interactive, π-stacking
GABRA2	beta-Sitosterol		-5.65	Hydrophobic interactive
FOS	Quercetin		-6.45	Hydrogen bonds, Hydrophobic interactive, π-stacking
FOS	Luteolin		-6.49	Hydrogen bonds, Hydrophobic interactive, π-stacking
FOS	Kaempferol		-7.26	Hydrogen bonds, Hydrophobic interactive, π-stacking
FOS	7-Methoxy-2-methyl-isoflavone		-6.27	Hydrogen bonds, Hydrophobic interactive, π-stacking
FOS	beta-Sitosterol		-5.43	Hydrophobic interactive

Note: Binding energy fuction [28]:

$$\Delta G_{\text{bind}} = C_{\text{lipo-lipo}} \sum f(r_{\text{tr}}) + C_{\text{hbond-neut-neut}} \sum g(\Delta r)h(\Delta \alpha) + C_{\text{hbond-neut-charged}} \sum g(\Delta r)h(\Delta \alpha) + C_{\text{hbond-charged-charged}} \sum g(\Delta r)h(\Delta \alpha) + C_{\text{max-metal-ion}} \sum f(r_{\text{lm}}) + C_{\text{rotb}} H_{\text{rotb}} + C_{\text{polar-phob}} V_{\text{polar-phob}} + C_{\text{coul}} E_{\text{coul}} + C_{\text{vdW}} E_{\text{vdW}} + \text{solvation terms}$$

Molecular docking data indicated that the binding capacity of GSK3B and luteolin (E) was significant.

4. Discussion

Under the current COVID-19 pandemic, many people with depression and insomnia may be related to environmental mutations and social anxiety. The study found that the symptom levels of depression, anxiety and insomnia in the quarantine area were significantly higher than those in the nonquarantine area, and they were at higher risk of depression, anxiety and insomnia, especially the severity of depression [30]. TCM believes that the main pathogenesis of insomnia is the imbalance of Qi and the inability of Yang to enter Yin. The Yellow Emperor's Internal Classic states, "If you are unable to make decisions, or if your emotions are not smooth, the liver qi will be stagnant, and the qi axis will not turn, but if you want to stretch, you will be inward. Disturb the soul and cause insomnia", and depression is due to stagnation of liver qi, so liver-regulating qi is the basic rule for the treatment of insomnia and depression, suggesting that qi-regulating drugs are potential drugs for the treatment of depression.

CHSGP is composed of 7 herbs: Chaihu, Xiangfu, Chuanxiong, Chenpi, Zhike, Baishao, and Gancao. Saikosaponin, the main chemical component of Chaihu, has sedative, antipyretic, immune enhancement, anti-inflammatory, antiviral, liver, and antitumor effects. The α -germanone of Xiangfu has an antidepressant-like effect [31], and Jiawei Xiangfu Decoction combined with acupuncture can significantly improve the sleep state of menopausal insomnia patients with liver stagnation and qi stagnation [32]. The main active ingredients of Chuanxiong have both a sedative effect [26] and the potential to improve depression. The antidepressant mechanism of Chenpi and its main active ingredients, chuanchenein, hesperidin and naringenin, is related to the improvement of neurobiochemical, neuroendocrine and neurotrophic systems [33]. Zhike exerts antidepressant effects mainly through its monoaminergic mechanism and prokinetic effects [34]. Fructus aurantii can enhance gastrointestinal motility by changing the expression level of 5-HT in the gastrointestinal tract of rats [35], suggesting that it can affect sleep to a certain extent. Paeoniflorin has neuroprotective and antidepressant biological activities, and it can treat related insomnia diseases through adenosine A1R to play a hypnotic effect [36]. Regulating the calmodulin/calmodulin-dependent protein kinase II (CaM/CaMKII) pathway and its downstream signaling molecules play an important role in the treatment and alleviation of affective disorders [37]. Glycyrrhizin can reduce IL-6 cytokines in brain tissue, and it is also a cytokine closely related to sleep/deprivation. IL-6 can inhibit the synthesis of IL-1 and reduce IL-6 cytokines, and then IL-1 increases synthesis, which in turn enhances the patient's nonrapid eye movement sleep time [38].

The results of the study showed that topological analysis identified the key components of quercetin, kaempferol, β -sitosterol, 7-methoxy-2-methyl isoflavones, luteolin, naringenin and other key components in CHSGP as the disease. It was the material basis for the treatment of insomnia and depression with the same treatment of different diseases. It had the largest number of targets and was also its core compound. Studies have shown that quercetin enhanced the hypnotic activity of pentobarbital in a dose-dependent manner by prolonging sleep time [39] and reducing anxiety and depression-like behaviors, immune dysfunction and brain oxidative stress [40], related to its improvement of neurotrophic function and anti-inflammatory effects [41]. Kaempferol has a wide range of pharmacological activities, which can reduce oxidative stress and proinflammatory cytokines, inhibit vascular endothelial inflammation [42], and have an effective antidepressant effect [26, 43]. Studies have found [44] that some Chinese herbal extracts contain β -sitosterol, which has anti-inflammatory, sedative and hypnotic activities [45]. Luteolin is a widely used flavonoid compound that has anti-anxiety and sleep-promoting effects [46]. Naringenin can activate Sirt1, enhance antioxidant capacity by reducing oxidative stress, and effectively improve inflammation and dopamine levels [47], thereby alleviating the pain caused by chronic sleep deprivation [48].

According to the drug-disease target intersection, CHSGP can treat insomnia and depression at the same time through 113 target proteins in different diseases. According to the degree value and the betweenness centrality, PPI analysis network topology analysis screened AKT1 and IL-6, and 42 core targets, such as IL1B, CASP3, and MAPK3, were mainly related to immunity, inflammation, oxidative stress, and neovascularization. AKT1 is involved in the regulation of processes such as metabolism, proliferation, growth and angiogenesis [49]. IL-6 is one of the most biologically active cytokines and can be called a sleepy mediator. Its circadian rhythm pattern reflects the steady-state drive of sleep [50], and increased IL-6 activity may cause depression by activating the hypothalamus-pituitary-adrenal axis or affecting neurotransmitter metabolism [51]. IL-1B protein is an important mediator of the inflammatory response, is involved in a variety of cell activities, such as cell proliferation, differentiation, and apoptosis, and is related to the diagnosis, specific symptoms, and antidepressant treatment response of major depression [1]. Caspase-3 (CASP3) belongs to the cysteine aspartic protease (Caspase) family of proteases and plays an irreplaceable role in the apoptosis pathway. Hippocampal apoptosis caused by sleep deprivation includes the number of apoptotic cells, caspase-3 activation, and Bax and Bcl-2 regulation [52]. MAPK3, called mitogen-activated protein kinase 3, is an important part of the MAP kinase signal transduction pathway and plays an important role in the cellular response cascade caused by extracellular stimulation. Another study [53] showed that the expression of the AKT1, MAPK3 and IL-6 genes in anxiety patients often increased significantly. The MCODE cluster analysis in the PPI network screened 7 core genes, including FOS, GABRA2, GSK3B, PON1, APOB, CYP1B1, and ADRA1A. FOS, also known as c-Fos, is a proto-oncogene that participates in cell growth, differentiation, information transmission, animal learning and memory and maintains wakefulness. Studies have shown that [54] FOS protein is involved in the normal differentiation, growth, learning, memory and other processes of cells, and it is more highly expressed in the brain endothelium, hippocampus, and striatum. GABA is found only in the nervous tissues of animals. It is an important inhibitory neurotransmitter and plays a role in the development process. It participates in a variety of metabolic activities and has high physiological activity. The GABRA2 gene encodes the GABAA-2 subunit, which is an ionotropic receptor related to anxiety, depression, and other behavioral disorders (including drug dependence and schizophrenia). Studies have found that [55] a higher expression level of $\alpha 2$ may have antidepressant effects through the signal transduction of GABAAR containing $\alpha 2$.

PPI network and GO analysis showed that the strong interactions of these target genes affected the synaptic membrane and postsynaptic membrane by participating in biological processes such as drug response, regulation of blood vessel diameter, and oxidative stress response, which included the molecular functions of synaptic membrane, postsynaptic membrane and its components, and which involved cell functions such as neurotransmitter receptor activity, postsynaptic neurotransmitter receptor activity, G protein coupled amine receptor activity, etc. The KEGG pathway enrichment analysis mainly involved the AGE-RAGE signaling pathway, neuroactive ligand-receptor interaction, IL-17 signaling pathway, TNF signaling pathway, endocrine resistance, Th17 cell differentiation, dopaminergic synapses, hepatitis B, Toll-like receptor signaling pathways and other signaling pathways related to inflammation, immunity, and oxidative stress.

Studies have found that the inhibition of the AGE/RAGE pathway and oxidative stress might be a possible mechanism by which melatonin exerts antidepressant and anti-anxiety effects in diabetic rats [56]. AGE-RAGE signaling is among the signaling pathways related to obstructive sleep apnea (OSA) [57]. A number of network pharmacology studies have found that TCM has neuroactive ligand-receptor interaction pathways in the treatment

of depression or insomnia [16, 58–60]. A literature study found that it might have a beneficial effect on the pathogenic conditions of the central nervous system by inhibiting the function of the IL-17 cytokine family [61].

The molecular docking results showed that the molecular docking in compounds (kaempferol, luteolin, quercetin, 7-methoxy-2-methyl isoflavone and beta-sitosterol) and five target proteins (AKT1, IL1B, IL-6, FOS, GSK3B, and GABRA) matched well, and the binding energy was less than -6 kcal/mol, which could form stable complexes and indirectly verified that these compounds had a regulatory effect on targets such as AKT1.

This study is aimed at the high incidence of global depression and insomnia under the current situation of the COVID-19 epidemic, and it is difficult to find effective prevention methods in clinical practice. At the same time, the network pharmacology of CHSGP provides us with an opportunity to explore the “Same Treatment for Different Diseases” potential pharmacological mechanism of CHSGP in treating insomnia and depression caused by the COVID-19 epidemic. Existing network pharmacology studies have screened 121 active ingredients and 15 depression-related targets of CHSGP from the database, mainly involving the regulation of neurotransmitters (serotonin, dopamine and adrenaline), the regulation of inflammatory mediators of TRP channels, calcium signaling pathway, cyclic adenosine monophosphate signaling pathway, and neural active ligand–receptor interaction, which are the channels through which signals play an antidepressant effect. It can have an antidepressant effect by improving neuronal plasticity, growth, transfer conditions and gene expression in neuronal cells and increasing the expression of gap junction proteins [16]. Animal experiments [62] confirmed that CHSGP can improve the depression-like behavior of rats exposed to chronic unpredictable mild stress (CUMS), possibly by inhibiting CHOP and caspase-12-mediated apoptosis of rat hippocampal cells. CHSGP can significantly improve the depression state of model rats by increasing the expression of BDNF and TrkB mRNA in the hippocampus, amygdala and frontal lobe [63]. A large number of clinical studies [64–66] have shown that CHSGP alone or combined with Western medicine has a significant effect on the treatment of insomnia, and network pharmacology data mining CHSGP may play a role in the treatment of insomnia through multiple components, multiple targets, and multiple pathways [67].

Although the research has some findings, it still has many limitations. First, due to incomplete information, the role of some CHSGP compounds in “Same Treatment for Different Diseases” may be ignored. Second, it is difficult to screen specific targets and key active ingredients directly from the complex cognitive CHSGP. Third, although CHSGP has antidepressant and sleep-improving effects in previous clinical studies and animal model experiments, its mechanism of action is still unclear, and further analysis and excavation are needed in subsequent clinical and animal experiments. Therefore, it is necessary to further study the role and specific targets and pathways of the important single components of the CHSGP in the process of treating insomnia and depression with the “Same Treatment for Different Diseases”.

5. Conclusions

In summary, this study used network pharmacology to find that the mechanism of CHSGP for insomnia and depression caused by the COVID-19 epidemic with “Same Treatment for Different Diseases” might be related to core targets such as AKT1, IL-6, IL1B, FOS, CASP3, MAPK3, and KEGG signaling pathways such as the AGE-RAGE pathway, neuroactive ligand–receptor interaction, and IL-17 signaling pathway. The results of molecular docking revealed that kaempferol, luteolin, quercetin and other compounds matched well with AKT1, IL1B, IL-6, FOS, GSK3B, GABRA and other target protein molecules. The overall analysis and verification of the relationship among CHSGP, insomnia and depression were the “Same Treatment for Different Diseases” relationship. In molecular biology research, in-depth pharmacological research and clinical application exploration of insomnia and depression provide a reference. However, this research is not perfect enough. It is necessary to carry out relevant clinical and animal experimental studies in the complex environmental background of the COVID-19 epidemic to verify its clinical efficacy and mechanism of action of CHSGP for insomnia and depression with the “Same Treatment for Different Diseases”.

Declarations

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Sacks D, Baxter B, Campbell B, et al. Multisociety Consensus Quality Improvement Revised Consensus Statement for Endovascular Therapy of Acute Ischemic Stroke[J]. *Int J Stroke*, 2018, 13(6):612-632. DOI: 10.1177/1747493018778713.
2. Marvaldi M, Mallet J, Dubertret C, et al. Anxiety, depression, trauma-related, and sleep disorders among healthcare workers during the COVID-19 pandemic: A systematic review and meta-analysis[J]. *Neurosci Biobehav Rev*, 2021, 126:252-264. DOI: 10.1016/j.neubiorev.2021.03.024.
3. Lang Q, Liu X, He Y, et al. Association between Working Hours and Anxiety/Depression of Medical Staff during Large-Scale Epidemic Outbreak of COVID-19: A Cross-Sectional Study[J]. *Psychiatry Investig*, 2020, 17(12):1167-1174. DOI: 10.30773/pi.2020.0229.
4. Huang Y, Zhou Y, Wei Y, et al. Differences in the Association of Anxiety, Insomnia and Somatic Symptoms between Medical Staff and the General Population During the Outbreak of COVID-19[J]. *Neuropsychiatr Dis Treat*, 2021, 17:1907-1915. DOI: 10.2147/NDT.S300719.
5. Zhang Z, Hu Y, Chen Y, et al. Sleep disorders and related factors among frontline medical staff supporting Wuhan during the COVID-19 outbreak[J]. *Bull Menninger Clin*, 2021 :1-17. DOI: 10.1521/bumc.2021_85_01.
6. Morin CM, Drake CL, Harvey AG, et al. Insomnia disorder[J]. *Nat Rev Dis Primers*, 2015, 1:15026. DOI: 10.1038/nrdp.2015.26.
7. Wang YS, Shen CY, Jiang JG. Antidepressant active ingredients from herbs and nutraceuticals used in TCM: pharmacological mechanisms and prospects for drug discovery[J]. *Pharmacol Res*, 2019, 150:104520. DOI: 10.1016/j.phrs.2019.104520.
8. Asarnow LD, Manber R. Cognitive Behavioral Therapy for Insomnia in Depression[J]. *Sleep Med Clin*, 2019, 14(2):177-184. DOI: 10.1016/j.jsmc.2019.01.009.
9. Liu L, Liu C, Wang Y, et al. Herbal Medicine for Anxiety, Depression and Insomnia[J]. *Curr Neuropharmacol*, 2015, 13(4):481-493. DOI: 10.2174/1570159x1304150831122734.
10. Riemann D, Krone LB, Wulff K, et al. Sleep, insomnia, and depression[J]. *Neuropsychopharmacology*, 2020, 45(1):74-89. DOI: 10.1038/s41386-019-0411-y.
11. Morin CM, Bjorvatn B, Chung F, et al. Insomnia, anxiety, and depression during the COVID-19 pandemic: an international collaborative study[J]. *Sleep Med*, 2021, 87:38-45. DOI: 10.1016/j.sleep.2021.07.035.
12. Unützer J, Klap R, Sturm R, et al. Mental disorders and the use of alternative medicine: results from a national survey[J]. *Am J Psychiatry*, 2000, 157(11):1851-1857. DOI: 10.1176/appi.ajp.157.11.1851.
13. Liu P, Yang P, Zhang L. Mode of Action of Shan-Zhu-Yu (*Cornus officinalis* Sieb. et Zucc.) in the Treatment of Depression Based on Network Pharmacology[J]. *Evid Based Complement Alternat Med*, 2020, 2020:8838888. DOI: 10.1155/2020/8838888.
14. Zhang YW, Cheng YC. Challenge and Prospect of Traditional Chinese Medicine in Depression Treatment[J]. *Front Neurosci*, 2019, 13:190. DOI: 10.3389/fnins.2019.00190.
15. Tang XS, Chen J, Fang G, et al. Discussion on the mechanism of Chaihu Shugan Powder in the treatment of insomnia based on network pharmacology[J]. *Chinese Modern Chinese Medicine*, 2021, 23(06):1013-1022.
16. Liu YY, Hu D, Fan QQ, et al. Mechanism of Chaihu Shugan Powder () for Treating Depression Based on Network Pharmacology[J]. *Chin J Integr Med*, 2020, 26(12):921-928. DOI: 10.1007/s11655-019-3172-x.
17. Xiao K, Li K, Long S, et al. Potential Molecular Mechanisms of Chaihu-Shugan-San in Treatment of Breast Cancer Based on Network Pharmacology[J]. *Evid Based Complement Alternat Med*, 2020, 2020:3670309. DOI: 10.1155/2020/3670309.
18. Guo H, Zhao CY, Zhan LB, et al. The mechanism of Liuwei Dihuang Pill in the treatment of hypertension, type 2 diabetes mellitus and Alzheimer's disease based on network pharmacology[J]. *Pharmacology and Clinic of Traditional Chinese Medicine*, 2021, 37(01):41-49.
19. Huang MW, Yang HJ, Zhou XC, et al. [Advances on network pharmacology in ethnomedicine research][J]. *Zhongguo Zhong Yao Za Zhi*, 2019, 44(15):3187-3194. DOI: 10.19540/j.cnki.cjcmm.20190711.201.

20. Luo TT, Lu Y, Yan SK, et al. Network Pharmacology in Research of Chinese Medicine Formula: Methodology, Application and Prospective[J]. *Chin J Integr Med*, 2020, 26(1):72-80. DOI: 10.1007/s11655-019-3064-0.
21. Ru J, Li P, Wang J, et al. TCMSP: a database of systems pharmacology for drug discovery from herbal medicines[J]. *J Cheminform*, 2014, 6:13. DOI: 10.1186/1758-2946-6-13.
22. UniProt: a worldwide hub of protein knowledge[J]. *Nucleic Acids Res*, 2019, 47(D1):D506-D515. DOI: 10.1093/nar/gky1049.
23. Szklarczyk D, Gable AL, Lyon D, et al. STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets[J]. *Nucleic Acids Res*, 2019, 47(D1):D607-D613. DOI: 10.1093/nar/gky1131.
24. Sun C, Yuan Q, Wu D, et al. Identification of core genes and outcome in gastric cancer using bioinformatics analysis[J]. *Oncotarget*, 2017, 8(41):70271-70280. DOI: 10.18632/oncotarget.20082.
25. Morris GM, Lim-Wilby M. Molecular docking[J]. *Methods Mol Biol*, 2008, 443:365-382. DOI: 10.1007/978-1-59745-177-2_19.
26. Rajeswari M, Santhi N, Bhuvaneshwari V. Pharmacophore and Virtual Screening of JAK3 inhibitors[J]. *Bioinformation*, 2014, 10(3):157-163. DOI: 10.6026/97320630010157.
27. Fazi R, Tintori C, Brai A, et al. Homology Model-Based Virtual Screening for the Identification of Human Helicase DDX3 Inhibitors[J]. *J Chem Inf Model*, 2015, 55(11):2443-2454. DOI: 10.1021/acs.jcim.5b00419.
28. Friesner RA, Banks JL, Murphy RB, et al. Glide: a new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy[J]. *J Med Chem*, 2004, 47(7):1739-1749. DOI: 10.1021/jm0306430.
29. Doncheva NT, Morris JH, Gorodkin J, et al. Cytoscape StringApp: Network Analysis and Visualization of Proteomics Data[J]. *J Proteome Res*, 2019, 18(2):623-632. DOI: 10.1021/acs.jproteome.8b00702.
30. Wang C, Song W, Hu X, et al. Depressive, anxiety, and insomnia symptoms between population in quarantine and general population during the COVID-19 pandemic: a case-controlled study[J]. *BMC Psychiatry*, 2021, 21(1):99. DOI: 10.1186/s12888-021-03108-2.
31. Xia B, Tong Y, Xia C, et al. α -Cyperone Confers Antidepressant-Like Effects in Mice via Neuroplasticity Enhancement by SIRT3/ROS Mediated NLRP3 Inflammasome Deactivation[J]. *Front Pharmacol*, 2020, 11:577062. DOI: 10.3389/fphar.2020.577062.
32. Yan XL, Yu YD, Yang DD. [Clinical efficacy of acupuncture combined with modified Xiangfu Decoction in treatment of menopausal insomnia cause by liver Qi stagnation][J]. *Zhongguo Zhong Yao Za Zhi*, 2020, 45(6):1460-1464. DOI: 10.19540/j.cnki.cjcmm.20191010.501.
33. Bansal Y, Singh R, Saroj P, et al. Naringenin protects against oxido-inflammatory aberrations and altered tryptophan metabolism in olfactory bulbectomized-mice model of depression[J]. *Toxicol Appl Pharmacol*, 2018, 355:257-268. DOI: 10.1016/j.taap.2018.07.010.
34. Zhang YJ, Huang W, Huang X, et al. Fructus Aurantii induced antidepressant effect via its monoaminergic mechanism and prokinetic action in rat[J]. *Phytomedicine*, 2012, 19(12):1101-1107. DOI: 10.1016/j.phymed.2012.05.015.
35. Jiang Y, Bai X, Zhu X, et al. The effects of Fructus Aurantii extract on the 5-hydroxytryptamine and vasoactive intestinal peptide contents of the rat gastrointestinal tract[J]. *Pharm Biol*, 2014, 52(5):581-585. DOI: 10.3109/13880209.2013.854396.
36. Yin D, Liu YY, Wang TX, et al. Paeoniflorin exerts analgesic and hypnotic effects via adenosine A1 receptors in a mouse neuropathic pain model[J]. *Psychopharmacology (Berl)*, 2016, 233(2):281-293. DOI: 10.1007/s00213-015-4108-6.
37. Song C, Wang J, Gao D, et al. Paeoniflorin, the Main Active Ingredient of Shuyu Capsule, Inhibits Ca(v)1.2 and Regulates Calmodulin/Calmodulin-Dependent Protein Kinase II Signalling[J]. *Biomed Res Int*, 2017, 2017:8459287. DOI: 10.1155/2017/8459287.
38. Huang Q, Wang YN, Han F, et al. Study on the potential mechanism of anti-insomnia effect of Guizhi Gancao Decoction based on network pharmacology[J]. *Journal of Hunan University of Traditional Chinese Medicine*, 2020, 40(04):452-459.
39. Ye MF, Liu Z, Lou SF, et al. Flos Albiziae aqueous extract and its active constituent quercetin potentiate the hypnotic effect of pentobarbital via the serotonergic system[J]. *Biomed Rep*, 2015, 3(6):835-838. DOI: 10.3892/br.2015.518.
40. Merzoug S, Toumi ML, Tahraoui A. Quercetin mitigates Adriamycin-induced anxiety- and depression-like behaviors, immune dysfunction, and brain oxidative stress in rats[J]. *Naunyn Schmiedeberg's Arch Pharmacol*, 2014, 387(10):921-933. DOI: 10.1007/s00210-014-1008-y.
41. Fang K, Li HR, Chen XX, et al. Quercetin Alleviates LPS-Induced Depression-Like Behavior in Rats via Regulating BDNF-Related Imbalance of Copine 6 and TREM1/2 in the Hippocampus and PFC[J]. *Front Pharmacol*, 2019, 10:1544. DOI: 10.3389/fphar.2019.01544.
42. Ren J, Lu Y, Qian Y, et al. Recent progress regarding kaempferol for the treatment of various diseases[J]. *Exp Ther Med*, 2019, 18(4):2759-2776. DOI: 10.3892/etm.2019.7886.
43. Gao W, Wang W, Peng Y, et al. Antidepressive effects of kaempferol mediated by reduction of oxidative stress, proinflammatory cytokines and up-regulation of AKT/ β -catenin cascade[J]. *Metab Brain Dis*, 2019, 34(2):485-494. DOI: 10.1007/s11011-019-0389-5.
44. Uddin G, Rauf A, Siddiqui BS, et al. Anti-nociceptive, anti-inflammatory and sedative activities of the extracts and chemical constituents of *Diospyros lotus* L[J]. *Phytomedicine*, 2014, 21(7):954-959. DOI: 10.1016/j.phymed.2014.03.001.
45. Liu WL, Wu BF, Shang JH, et al. *Moringa oleifera* Lam Seed Oil Augments Pentobarbital-Induced Sleeping Behaviors in Mice via GABAergic Systems[J]. *J Agric Food Chem*, 2020, 68(10):3149-3162. DOI: 10.1021/acs.jafc.0c00037.
46. Kim TH, Custodio RJ, Cheong JH, et al. Sleep Promoting Effect of Luteolin in Mice via Adenosine A1 and A2A Receptors[J]. *Biomol Ther (Seoul)*, 2019, 27(6):584-590. DOI: 10.4062/biomolther.2019.149.

47. Olufunke D, Edidiong A, Oluwatomisin F, et al. Therapeutic activities of naringenin on efavirenz-induced sleep-like disorder in the midbrain of white albino mice[J]. *Iran J Basic Med Sci*, 2020, 23(11):1462-1470. DOI: 10.22038/ijbms.2020.47043.10852.
48. Arora S, Venugopalan A, Dharavath RN, et al. Naringenin Ameliorates Chronic Sleep Deprivation-Induced Pain via Sirtuin1 Inhibition[J]. *Neurochem Res*, 2021, 46(5):1177-1187. DOI: 10.1007/s11064-021-03254-9.
49. Palumbo S, Paterson C, Yang F, et al. PKB β /AKT2 deficiency impacts brain mTOR signaling, prefrontal cortical physiology, hippocampal plasticity and select murine behaviors[J]. *Mol Psychiatry*, 2021, 26(2):411-428. DOI: 10.1038/s41380-020-00964-4.
50. Vgontzas AN, Bixler EO, Lin HM, et al. IL-6 and its circadian secretion in humans[J]. *Neuroimmunomodulation*, 2005, 12(3):131-140. DOI: 10.1159/000084844.
51. Ting EY, Yang AC, Tsai SJ. Role of Interleukin-6 in Depressive Disorder[J]. *Int J Mol Sci*, 2020, 21(6). DOI: 10.3390/ijms21062194.
52. Zuo JX, Li M, Jiang L, et al. Hydrogen Sulfide Prevents Sleep Deprivation-Induced Hippocampal Damage by Upregulation of Sirt1 in the Hippocampus[J]. *Front Neurosci*, 2020, 14:169. DOI: 10.3389/fnins.2020.00169.
53. Liu FX, Lin ZX, Zhang HL, et al. Analysis of the mechanism of Jiawei Guipi Decoction in the treatment of Yin-fire insomnia with anxiety based on network pharmacology[J]. *Chinese Journal of Experimental Formulas*, 2020, 26(20):161-168.
54. Wang TX, Wei HH, Chen ZK, et al. Hypnotic activities of Zao Ren An Shen capsule, a traditional Chinese medicine, in an anxiety-like mouse model[J]. *Sleep Breath*, 2020 . DOI: 10.1007/s11325-020-02244-5.
55. Benham RS, Hewage NB, Suckow RF, et al. Prodepressant- and anxiogenic-like effects of serotonin-selective, but not noradrenaline-selective, antidepressant agents in mice lacking α 2-containing GABA(A) receptors[J]. *Behav Brain Res*, 2017, 332:172-179. DOI: 10.1016/j.bbr.2017.05.063.
56. Ergenc M, Ozacmak HS, Turan I, et al. Melatonin reverses depressive and anxiety like-behaviours induced by diabetes: involvement of oxidative stress, age, rage and S100B levels in the hippocampus and prefrontal cortex of rats[J]. *Arch Physiol Biochem*, 2019 :1-9. DOI: 10.1080/13813455.2019.1684954.
57. Jagannathan R, Seixas A, St-Jules D, et al. Systems Biology Genetic Approach Identifies Serotonin Pathway as a Possible Target for Obstructive Sleep Apnea: Results from a Literature Search Review[J]. *Sleep Disord*, 2017, 2017:6768323. DOI: 10.1155/2017/6768323.
58. Xiong WC, Wu HZ, Xiong YY, et al. Network Pharmacology-based Research of Active Components of Albiziae Flos and Mechanisms of Its Antidepressant Effect[J]. *Curr Med Sci*, 2020, 40(1):123-129. DOI: 10.1007/s11596-020-2155-7.
59. Jia Y, Zou J, Wang Y, et al. Action mechanism of Roman chamomile in the treatment of anxiety disorder based on network pharmacology[J]. *J Food Biochem*, 2021, 45(1):e13547. DOI: 10.1111/jfbc.13547.
60. Jin D, Zhang J, Zhang Y, et al. Network pharmacology-based and molecular docking prediction of the active ingredients and mechanism of ZaoRenDiHuang capsules for application in insomnia treatment[J]. *Comput Biol Med*, 2021, 135:104562. DOI: 10.1016/j.combiomed.2021.104562.
61. Waisman A, Hauptmann J, Regen T. The role of IL-17 in CNS diseases[J]. *Acta Neuropathol*, 2015, 129(5):625-637. DOI: 10.1007/s00401-015-1402-7.
62. Sun KH, Jin Y, Mei ZG, et al. Antidepressant-Like Effects of Chaihu Shugan Powder on Rats Exposed to Chronic Unpredictable Mild Stress through Inhibition of Endoplasmic Reticulum Stress-Induced Apoptosis[J]. *Chin J Integr Med*, 2021, 27(5):353-360. DOI: 10.1007/s11655-020-3228-y.
63. Deng Y, Zhang CH, Zhang HN. Effects of chaihu shugan powder on the behavior and expressions of BDNF and TrkB in the hippocampus, amygdala, and the frontal lobe in rat model of depression [J]. *Zhongguo Zhong Xi Yi Jie He Za Zhi*, 2011, 31(10):1373-1378.
64. LIN C,, LI YH. Clinical observation on the treatment of insomnia after mild craniocerebral trauma with Chaihu Shugan San modified formula [J]. *Journal of Guangzhou University of Traditional Chinese Medicine*, 2021, 38(05):890-894.
65. Yu M, Wang YC, Li L, et al. Clinical effect of abdominal acupuncture combined with Chaihu Shugan powder in the treatment of perimenopausal insomnia due to qi stagnation [J]. *China Medical Herald*, 2020, 17(20):160-163.
66. Zhang HZ, Zhu XD, Zhang JX, et al. Observation on the curative effect of Chaihu Shugan Powder combined with Eszopiclone Tablets on insomnia due to liver stagnation and qi stagnation [J]. *TCM Research*, 2016, 29(06):5-7.
67. Yang DF, Cao LP. Clinical observation on the treatment of insomnia due to liver stagnation with modified Chaihu Shugan Powder [J]. *Western Traditional Chinese Medicine*, 2015, 28(11):82-84.

Figures

Figure 1

The experimental flow of this study.

Figure 2

Guijing analysis of each Chinese medicine in CHSGP

Figure 5

Topological analysis of common targets among CHSGP, insomnia and depression

Figure 6

The histogram and bubble chart of GO enrichment and KEGG pathway analysis among CHSGP and insomnia and depression. (A)The histogram of GO enrichment analysis(BP, MF, CC). (B) The bubble of GO enrichment analysis (BP, MF, CC). (C)The histogram of KEGG pathway analysis. (D)The bubble of KEGG pathway analysis.

Figure 7

CHSGP and insomnia, depression component-disease-pathway-target network construction

Figure 8

Chord diagram of the relationship in the KEGG pathways and targets among CHSGP, insomnia and depression

Figure 9

3D molecular docking diagrams of active ingredients and targets. (A) AKT1 and Kaempferol, (B) IL1B and quercetin, (C) IL6 and kaempferol, (D) AKT1 and stigmasterol, (E) GSK3B and luteolin, (F) GSK3B and 7-methoxy-2-methyl-isoflavone, and (G) GSK3B and beta-sitosterol.