doi.org/10.36721/PJPS.2026.39.1.REG.13817.1

Research on neuroimmune regulatory mechanisms and intervention strategies for chronic insomnia based on network pharmacology

Yun Lu
The First College of Clinical Medical Science, China Three Gorges University and Yichang Central People's Hospital, Yichang, Hubei, China

Abstract: **Background**: Chronic insomnia impairs health-related quality of life and current pharmacotherapies carry substantial adverse-effect profiles, prompting the search for safer multi-target interventions. Kong Sheng Pillow Zhongdan (KSPZ), a classical herbal formula, is empirically used for sleep disturbance, yet its molecular basis remains unclear. **Objectives**: To elucidate the putative mechanisms of KSPZ against chronic insomnia through a network-pharmacology approach and to prioritise targets for experimental validation. **Methods**: Active compounds were retrieved from TCMSP, HIT2.0 and TCMIP and filtered by oral bioavailability ≥30% and blood – brain barrier permeability ≥ – 0.3. Insomnia-related genes were collected from DisGeNET, GeneCards and OMIM. Overlapping targets defined the "core prescription–insomnia" interactome (126 genes). Protein–protein interaction networks were constructed with STRING and hub nodes identified by CytoHubba. GO, KEGG and Reactome enrichment analyses were performed with clusterProfiler; key ligand–target pairs were evaluated by AutoDock Vina. A drug–ingredient–target–disease network was visualised in Cytoscape. **Results**: Twenty-eight bioactive compounds (e.g., quercetin, kaempferol, luteolin) were mapped to 126 shared targets enriched in neuro-inflammation (IL-17, TNF, NF-κB), serotonergic and dopaminergic synapses, circadian rhythm and cAMP signalling. Top hub genes included TNF, IL6, AKT1, PTGS2, BDNF and DRD2. Molecular docking showed high affinities ($\Delta G \leq -8.5$ kcal mol^{-1}) for quercetin–GABRA1, kaempferol–HTR2A and luteolin–BDNF complexes, supporting modulatory effects on inhibitory/excitatory neurotransmission and neuroplasticity. **Conclusion**: KSPZ exerts multi-level effects on neuro-immune regulation, inflammation and circadian pathways, providing a rational basis for its empirical use in chronic insomnia. In-vivo validation of the predicted neurotransmitter and cytokine targets is warranted to translate these network findings into clinical applications.

Keywords: Biological functioning; Chronic insomnia; Intervention strategies; Network pharmacology; Sleep disorders

Submitted on 06-12-2024 – Revised on 16-04-2025 – Accepted on 16-04-2025

INTRODUCTION

Chronic insomnia, a prevalent and persistent sleep and wakefulness disorder, is increasingly affecting individuals worldwide, leading to significant negative impacts on their physical and mental health as well as their quality of life (Martinez *et al*., 2024; Dressle *et al*., 2022). The etiology of chronic insomnia is highly complex, encompassing neurotransmitter imbalances, psychological factors, lifestyle habits and various physiopathological changes. The condition presents with a diverse range of phenotypes and its pathogenesis remains to be fully elucidated (Shuai, 2023; He *et al*., 2022). Current clinical interventions for chronic insomnia face numerous limitations, such as potential side effects, suboptimal long-term efficacy and significant individual differences in drug responses. Additionally, psychotherapy and lifestyle modifications often demand high levels of patient compliance and self-management, posing practical challenges in their implementation (Mittal *et al*., 2024). Therefore, the search for safe, effective, easily promotable and low-cost treatments is of utmost importance for addressing chronic insomnia (Fernandes *et al*., 2024).

In recent years, the potential therapeutic role of traditional Chinese medicine (TCM) compounds in treating chronic insomnia has garnered increasing attention. Kong Sheng Pillow Zhongdan, a well-known TCM compound with a long history and wide range of sources, has demonstrated certain therapeutic effects on chronic insomnia in clinical practice. However, the specific mechanisms underlying its efficacy remain unclear. Network pharmacology offers a novel perspective and a powerful tool for investigating the intricate mechanisms of drug treatments for chronic insomnia. This approach involves searching for active ingredients in the four Chinese medicines that constitute Kong Sheng Pillow Zhongdan using seven databases, including the Traditional Chinese Medicine Systems Pharmacology Database (TCMSP), Herbal Ingredients Targets Database (HIT2.0) and Traditional Chinese Medicine Integrated Pharmacology Database (TCMIP). The active ingredients are then screened based on criteria such as oral bioavailability and blood-brain barrier permeability. Target information is obtained through the Uniprot database. Related targets are searched from five databases and used to construct a drug-ingredient-target-disease network and a protein interaction network. Multiple platforms are employed for bioprocess analysis, intersecting gene annotation and molecular docking. This

**Corresponding author:* e-mail: luyun1987113@163.com

comprehensive analysis aims to systematically elucidate the complex relationships between the drug components of Kong Sheng Pillow Zhongdan and the targets associated with chronic insomnia, revealing its potential mechanisms of action and providing a theoretical basis for developing more effective treatment strategies for chronic insomnia.

MATERIALS AND METHODS

Data collection and screening

The active ingredients and targets of Kong Sheng Pillow Zhongdan were identified using several databases, including the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, http://lsp.nwu.cn/temsp.php), the TCM Ingredient Target Platform (HIT2.0, http://hit2.badd-cao.net), the TCM Integrated Pharmacology Research Platform (TCMIP, http://hit2.badd-cao.net), the TCM Integrated Database (TCMID, http://www.megabionet.org/tcmid/), the Organic Small Molecule Bioactivity Database (PubChem, http://pubchem.ncbi.nlm.nih.gov/), the Taiwan Traditional Chinese Medicine Database (TCMDatabase@Taiwan, http://tcm.cmu.edu.tw) and the Chinese Natural Products Chemical Composition Database (https://pharmdata.ncmi.cn/cnpe). These databases were used to search for the active ingredients of the four traditional Chinese medicines in Kong Sheng Pillow Zhongdan: Yuanzhi, Shikamushi Tortoise Plate and Longzhi. The selection criteria included oral bioavailability (OB ≥ 30%), blood-brain barrier permeability (BBB ≥ -0.3) and drug-likeness (DL ≥ 0.1). The target information was obtained from the Uniprot database (https://www.uniprot.org/) by specifying the species as human (Homo sapiens).

Experimental methodology

Screening of Active Ingredients and Their Targets

The active ingredients and their targets of Kong Sheng Pillow Zhongdan were identified using the TCMSP database with the criteria of oral bioavailability (OB ≥ 30%) and drug-likeness (DL ≥ 0.18). The Uniprot database was used to annotate the target genes of the traditional Chinese medicines, focusing on human targets. This process generated a drug-component-target-disease network diagram.

Prediction of insomnia and amnesia-related targets

The GeneCards database was used to identify insomnia-related targets by searching for genes associated with insomnia. The intersection of these targets with the potential targets of Kong Sheng Pillow Zhongdan was mapped to identify the potential targets for treating insomnia. GeneCards is a comprehensive database providing detailed information on human genes, including genomic, transcriptomic, proteomic, genetic, clinical and functional data.

Drug-component-target-disease network construction

The intersection of the active ingredient targets of Kong Sheng Pillow Zhongdan and the disease-related targets of insomnia and amnesia was used to identify common targets. A drug-component-target-disease network was constructed, with nodes representing drugs, active ingredients, targets and diseases and edges representing the relationships between these nodes. The importance of the nodes was evaluated using degree and meso-centrality measures.

Protein interaction network construction and key target screening

The STRING database was used to analyze the potential targets of Kong Sheng Pillow Zhongdan for treating insomnia and amnesia. The interactions of common target proteins were visualized and topologically analyzed using Cytoscape 3.7.1 software. Key targets were identified based on their connectivity and centrality measures.

Bioprocess analysis

The shared targets were analyzed using a platform to obtain results "*Complex network analysis"* on biological processes, molecular functions, cellular components and KEGG pathway enrichment analysis.

Biomolecular functional annotation of intersecting genes

The Metascape database was used to perform GO annotation analysis and KEGG pathway enrichment analysis on the intersecting genes of Kong Sheng Pillow Zhongdan and chronic insomnia. The analysis was conducted with a MinOverlap of 3 and a significance threshold of $P \leq 0.01$, yielding information on molecular functions (MF), biological processes (BP) and cellular components (CC).

Cluster analysis

Hierarchical clustering was performed to identify high-frequency medications and summarize the core Chinese medicines of Kong Sheng Pillow Zhongdan. Frequency analysis was used to summarize the formula pattern for treating insomnia.

Complex network analysis

The complex network analysis module of the medical case cloud platform was used to analyze the core prescription of Kong Sheng Pillow Zhongdan for insomnia. The hierarchical network algorithm was applied to classify the drugs hierarchically.

Analysis of immunoregulatory mechanisms

Screening results of active ingredients of Dan in Kong Sheng Pillow

The active ingredients of Zhongdan in Kung Sheng Pillow were selected as Atractylodes macrocephala 23, Cyperus rotundus 46, Pinellia ternata 172, Poria cocos 30, Calamus calamus 75, Jujubae jujubae 32, Semen coix lacryma 76, Polygala farfarae 55. The target annotations for each

component of Kong Sheng Pillow Zhongdan are 18 for Atractylodes macrocephala, 40 for Phellodendron Bidentata, 127 for Pinellia, 21 for Poria, 103 for Acorus calamus, 46 for Jujubae-jujubae, 62 for Semen Coix lacryma, 46 for Polygonum multiflorum and a total of 134 targets were merged by deleting duplicates of the above mentioned target points. A total of 134 targets were deleted from the above targets and 19 active ingredients were obtained from each of the Chinese medicines in Kung Sheng Pillow Zhongdan. The main active ingredients of Kung Sheng Pillow Zhongdan are shown in Table 1 and the highest oral bioavailability is Atractylodes macrocephala, which reaches 54.18% and the pharmacological properties of carvacrol and stigmasterol in Bupleurum officinale are the highest, which are 0.81 and 0.76, respectively, indicating that there exists a certain degree of efficacy in chronic insomnia.

Acquisition of disease-related targets and intersecting genes

Core prescription and insomnia targets were obtained through Genecards, Figure 1 shows drug-disease related targets the number of relevant targets for disease was 6,715 and there were a total of 126 genes that intersected with insomnia targets for potential targets of action of core prescription.

Fig. 2 shows the drug-effective compound-disease target interaction network, this network includes a total of 381 nodes and 1779 edges. Degree value is a key indicator of the importance of the nodes and the topology of the network was analyzed by network analyze and the average drgee value in the network was 6.79. Among the top five compounds with degree value were dermatophyllin (MOL000098), B-sitosterol (MOL000358) kaempferol (MOL000422), stigmasterol (MOL000449) and baicalein (MOL002714). The top five targets with degree values were PTGS2, PTGS1, NCOA2, PRKACA and SCN5A.This suggests that the joint action of multiple targets exemplifies the complexity of drug therapy for insomnia. After importing the intersecting targets into the STRING database, the protein-protein interaction relationships were initially obtained and then the PPI network was constructed using Cytoscape and adjusted according to the drgee value. The network has 126 nodes, 1425 edges and the average degree value is 22.98. The color and size are adjusted according to the degree value. Applying ytoHubba plugin and using MCC algorithm for calculation, the top ten Hub genes were VEGFA, IL6, TNF, AKT1, CASP3, MMP9, IL1B, IL10, CXCL8 and PPARG, which may be the core genes for insomnia treatment.

Then the Metascape database was applied to GO analysis of 126 targets and 4774 entries, 427 CC entries and 681 MF entries were obtained and their top 10 entries were visualized, respectively and the results of GO analysis are shown in Fig. 3. Biological processes (BP) are mainly involved in cellular response to nitrogen compounds (B1), cellular response to organic cyclic compounds (B2), blood circulation (B3), cellular response to lipids (B4), response to inorganic substances (B5), chemical synapses (B6), response to exogenous stimuli (B7), positive regulation of cellular motility (B8), intracellular homeostasis (B9), phosphorylation of the positive regulation (B10). Cellular Composition (CC) mainly involves membrane rafts (C1), synaptic membranes (C2), receptor complexes (C3), plasma membrane protein complexes (C4), transcriptional regulatory complexes (C5), dopaminergic synapses (C6), vesicle lumens (C7), outer plasma membranes (C8), neuronal projection cytoplasm (C9) and the 5-hydroxytryptamine receptor complex (C10). Molecular functions (MF) mainly involve G protein-coupled amine receptor activity chloride (M1), monatomic cation transporter activity (M2), neurotransmitter receptor activity (M3), DNA-binding transcription factor binding (M4), nuclear receptor activity (M5), cytokine receptor binding (M6), channel activity (M7), amine binding (M8), catecholamine binding (M9), protein homodimerization activity (M10). Reflecting the multi-target and multi-pathway nature of herbal medicine in treating diseases, it can reduce the number of awakenings and ensure the integrity of sleep.

Molecular docking results

Table 2 shows the parameters of the main active ingredients of Kung Sheng Pillow Zhongdan, the network node characteristic parameters found that kaempferol has the highest connectivity of 17, which is the main ingredient of Kung Sheng Pillow Zhongdan, the mediator degree of kaempferol is 0.233 254 65, the density of nodes is 0.433 673 48 and the mediator degree of amino acid residues and kaempferol is the closest 0.057 175 79, which is the occurrence of hydrogen bonding. Kong Sheng pillow Zhongdan may act on targets such as RELA through active ingredients such as kaempferol, thus achieving the effect of insomnia treatment.

Bioprocess enrichment analysis

SCPE's in-depth investigation of the molecular mechanisms of treating insomnia and amnesia, GO functional analysis was done separately for the targets, which resulted in the potential functional modules for treating insomnia and amnesia in SCPE and the possible interaction mechanisms of each drug occurring in the model and the specific effects and importance of different drugs in various biological processes were identified.

Each modular network was analyzed using CO enrichment, while the first 3 relevant entries of each MODE module were parsed and the module entries for the biological functions of treating insomnia and amnesia are shown in Table 3. The results show that SCPE treatment of insomnia and amnesia is mainly closely related to cellular response to organic circulating compounds, hormonal response and blood circulation. The results of the analysis specific to each drug are as follows:

Table 1: Main active ingredients of Kongsheng Zhenzhong Dan

Drug	NO	Molecular number	Molecular number	Oral bioavailability (%)	Drug-like properties
Atractylodes macrocephala	BZ	MOL000049	3β-acetoxyatractylone	54.18	0.22
Pine nuts	BZR	MOL001439	Arachidonie acid	45.67	0.20
	BX1	MOL002670	Cavidine	35.74	0.81
	BX2	MOL002714	Baicalein	33.62	0.21
Pinellia	BX3	MOL000358	β-Beta-sitosterol	37.01	0.75
	BX4	MOL000449	Stigmasterol	43.93	0.76
	BX5	MOL000519	Coniferin	31.21	0.32
Poria	FL	MOL000296	Hederagenin	37.01	0.75
Acorus calamus	SCP1	MOL000422	Kaempferol	41.98	0.24
	SCP2	MOL003542	8-sopentenyl-aempferol	38.14	0.39
	SZR1	MOL001522	(T)(S)-Coclaurine	42.45	0.24
Chinese date seed	SZR2	MOL001542	Swertisin	31.93	0.75
	SZR3	MOL001546	Zizyphusine	41.63	0.55
	YYR1	MOL000298	Ergosterol	14.39	0.72
Job's tears	YYR2	MOL000449	Stigmasterol	43.93	0.76
	YYR3	MOL001323	α1-Sitosterol alphal	43.38	0.78
	YYR4	MOL001884	Omaine	26.72	0.51
Polygala	YZ1	MOL001997	5,6,7-Trimethoxyeoumarin	/	/
	YZ2	MOL009578	(Z)-3-(3,4,5-rime-thoxyphenyl) acrylie acid	/	/

Table 2: Parameters of the main active ingredients of Kongsheng Zhenzhong Dan

Component coding	Name	Degree	Betweenness	Node closeness
MOL000422	Kaempferol	17	0.233 254 65	0.433 673 48
MOL002714	Baicalein	13	0.057 175 79	0.357 142 87
MOL001439	Arachidonie acid	10	0.092 262 19	0.354 166 68
MOL002670	Cavidine	9	0.061 707 93	0.277 777 79
MOL001522	(S)-Coclaurine	9	0.049 129 29	0.307 971 01

Table 3: Module entries for biological functions of treating insomnia and amnesia

Module network	Entry notes
SCPEFTNAL	G0:0071407|cellular response to organic cyclic compound|-27.6
	G0:0009725|response to hormone|-27.1
	G0:0008015|blood circulation|-21.0
MCODE ALL	hsa04080|Neuroactive ligand-receptor interaction|-21.1
	R-HSA-388396lGPCR downstream signalling|-20.5
	R-HSA-372790lSignaling by GPCR|-19.6
MCODE 1	G0:0008503lbenzodiazepine receptor activity|-11.5
	G0:00228511GABA-gated chloride ion channel activity|-11.2
	G0:0005237 linhibitory extracellular ligand -gated ion channel activity|-10.9
MCODE 2	G0:0030522|intracellular receptor signaling pathway|-15.4
	G0:0009725|response to hormone|-12.8
	G0:0035357|peroxisome proliferator activated receptor signaling pathway|-12.6
MCODE 3	R-HSA-375280|Amine ligand-binding receptors|-16.5
	G0:0008227|G protein-coupled amine receptor activity|-15.9
	R-HSA-416476|G alpha(q)signalling events|-15.1
MCODE 4	R -HSA -966082|ADORA2Bmediatedanti -inflammatory cytokines production|-9.4
	G0:0007189|adenylate cyclase -activating G protein -coup|edreceptor signaling pathway|-9.3
	R-HSA-418555|G alpha(s)signalling events|-9.2
MCODE 5	G0:0031625|ubiquitin protein ligase binding|-6.0
	G0:0044389|ubiquitin-like protein ligase binding|-5.9
	G0:0030155|regulation of cell adhesion|-4.8
MCODE 6	hsa00350|Tyrosine metabolism|-8.8
	hsa00982|Drug metabolism- cytochrome P450|-7.9.
	R-HSA-211945|Phase I - Functionalization of compounds|-7.4
Shichangpu	hsa04080|Neuroactive ligand-receptor interaction|-21.7
	G0:0071407|cellular response to organic cyclic compound|-20.6
	G0:0030594|neurotransmitter receptor activity|-20.5
yuanodi	G0:0009725|response to hormone|-14.6
	G0:1901699|cellular response to nitrogen compound|-14.1
	G0:0071407|cellular response to organic cyclic compound|-14.0
guiban	R-HSA-375280|Amine ligand-binding receptors|-10.5
	G0:0008227|G protein-coupled amine receptor activity|-10.0
	G0:0035296|regulation of tube diameter|-9.8
longeu	hsa04210|Apoptosis|-10.9
	G0:0043523|regulation of neuron apoptotic process|-9.8
	hsa04215|Apoptosis - multiple species|-9.1

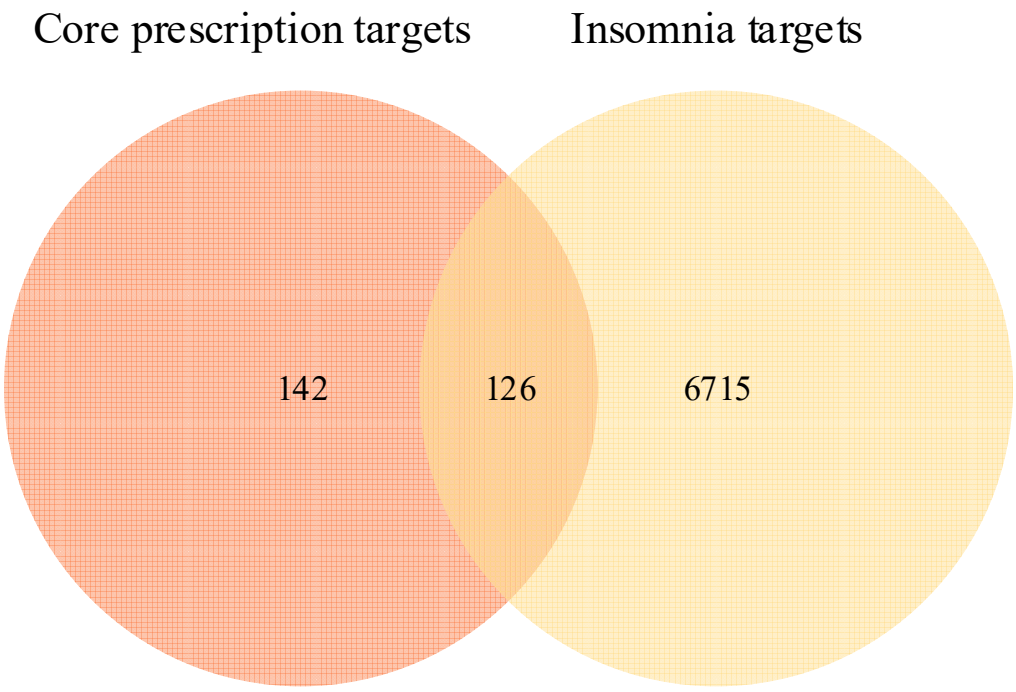


Fig. 1: Drug-disease related targets

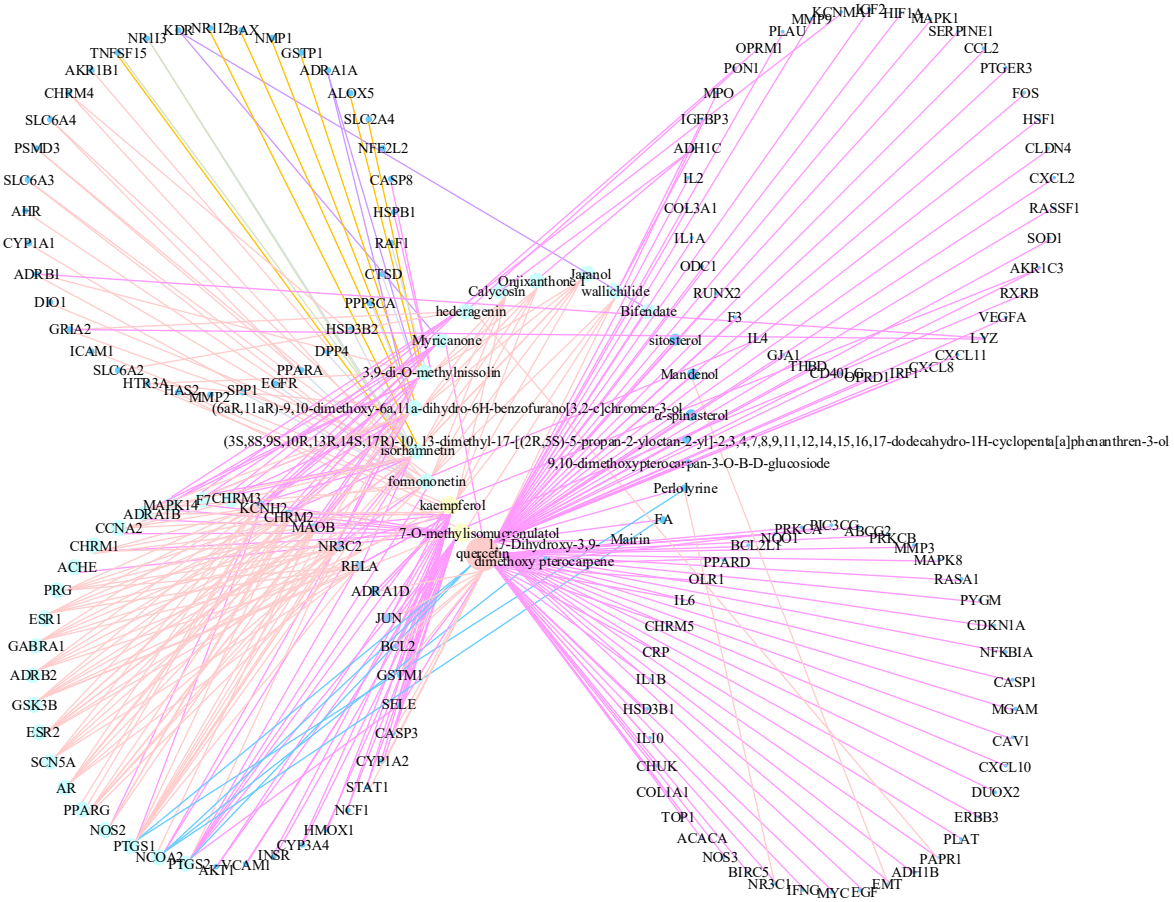


Fig. 2: Drug-active ingredient-disease target network

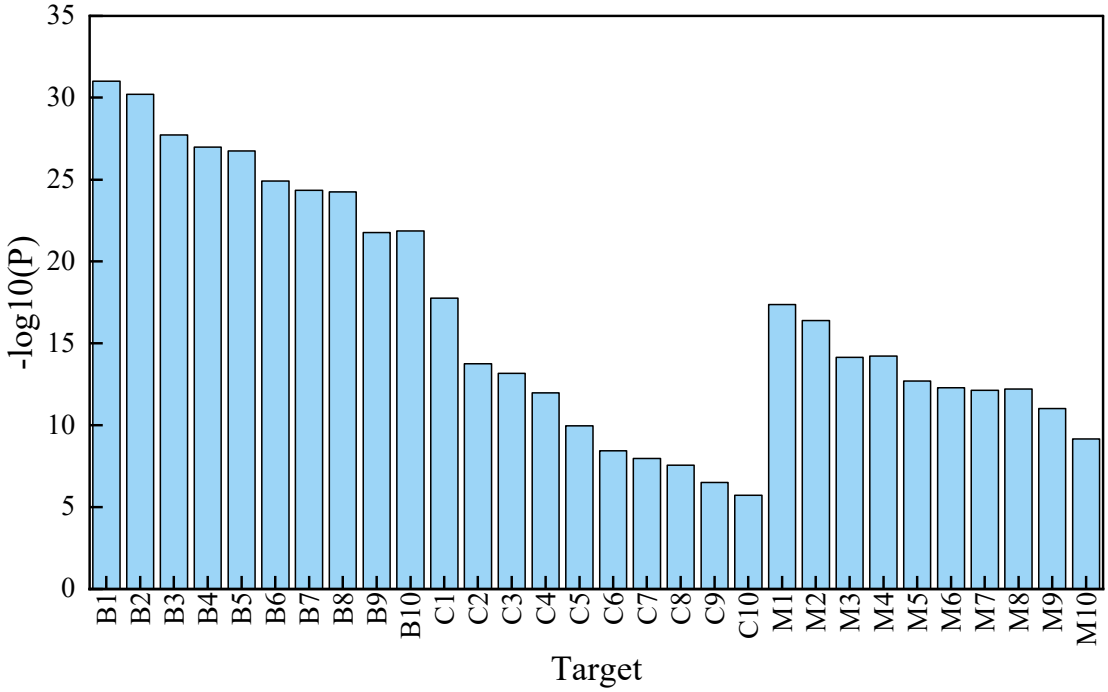


Fig. 3: GO analysis results

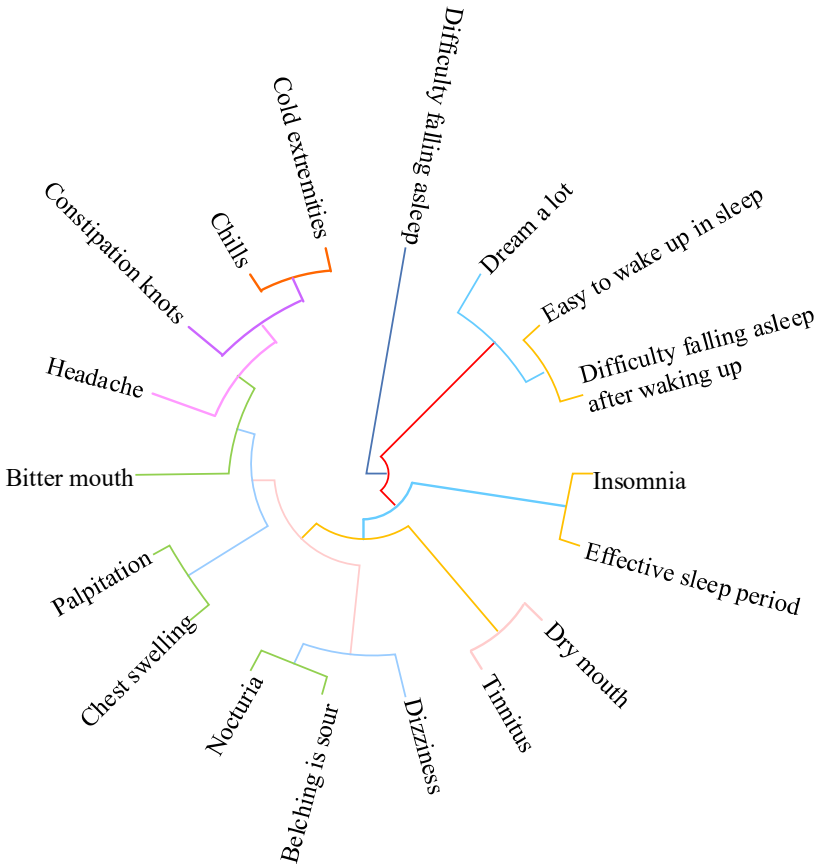


Fig. 4: Symptom system aggregation

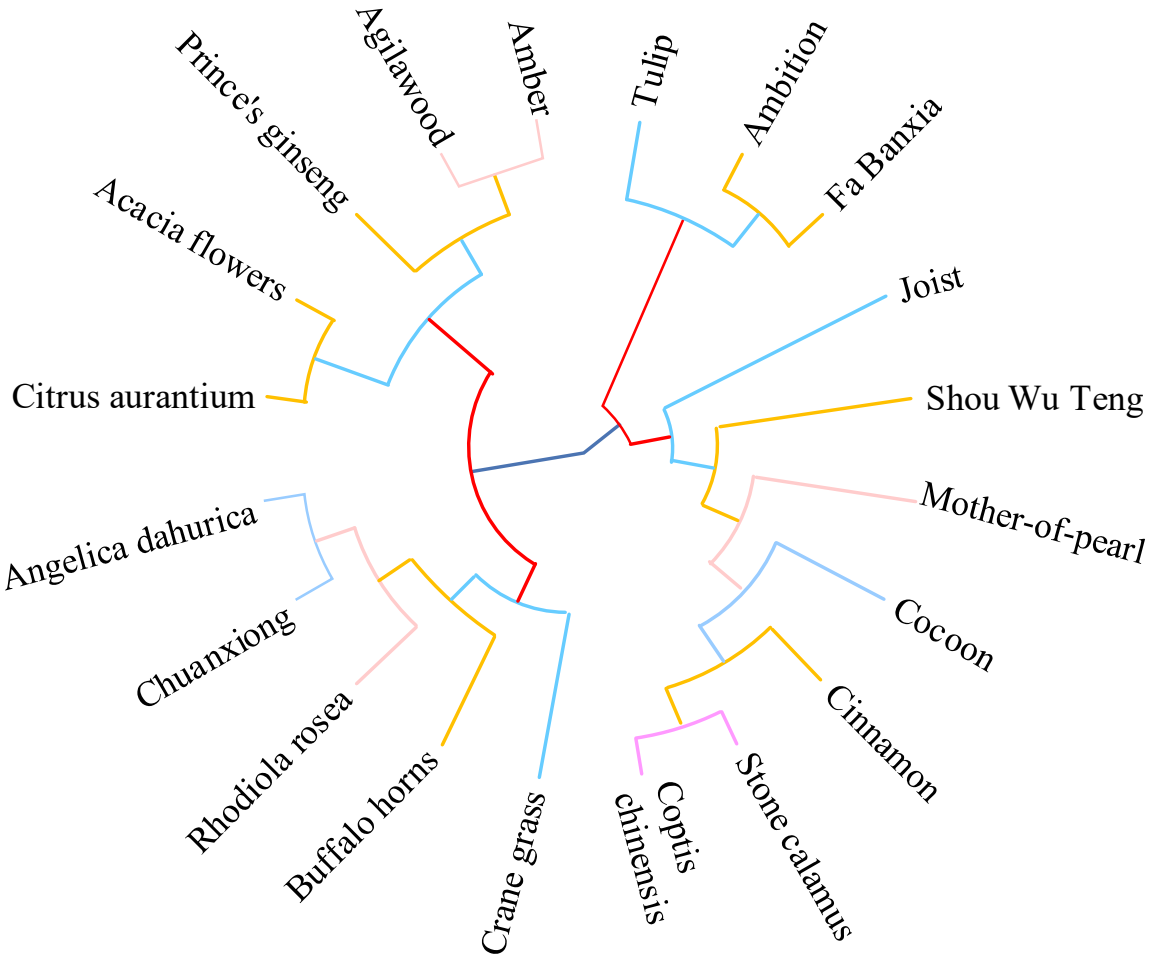


Fig. 5: Drug system aggregation

(1) Calamus target mainly interfered with the process of neuroactive ligand-receptor interaction, cellular response to organic circulating compounds and neurotransmitter receptor activity, which helped to regulate insomnia condition.

(2) The target point of Yuanzhi mainly regulates the process of response to hormones and cellular response to ammonia and organic circulating compounds and influences the immune response through the endocrine and immune axes to improve the sleep condition.

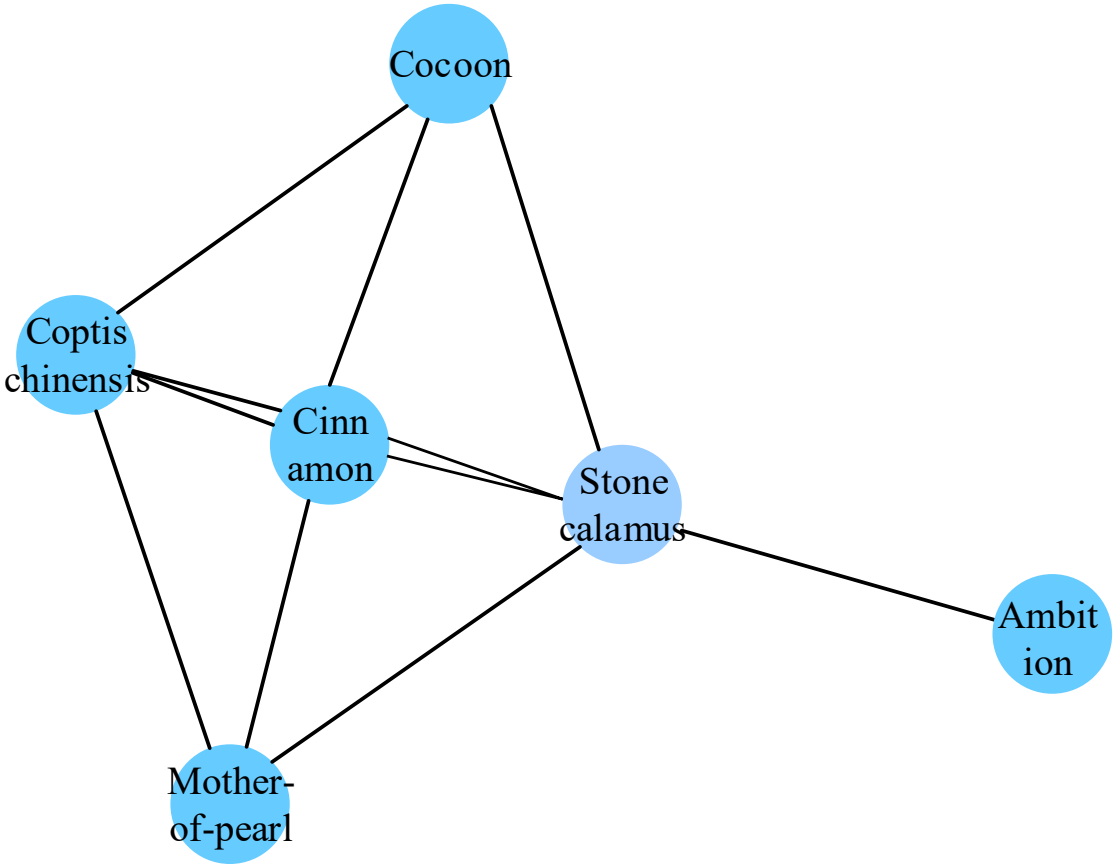
(3)Tortoise target point mainly affects amine receptor ligand binding and G protein-coupled amine receptor activity and tubulin regulation response process, which can improve the state of neuromodulation and thus regulate sleep.

(4) The keikaku target point mainly mediates apoptosis and regulates neuronal apoptosis process, which not only improves insomnia symptoms, but also contributes to physical health.

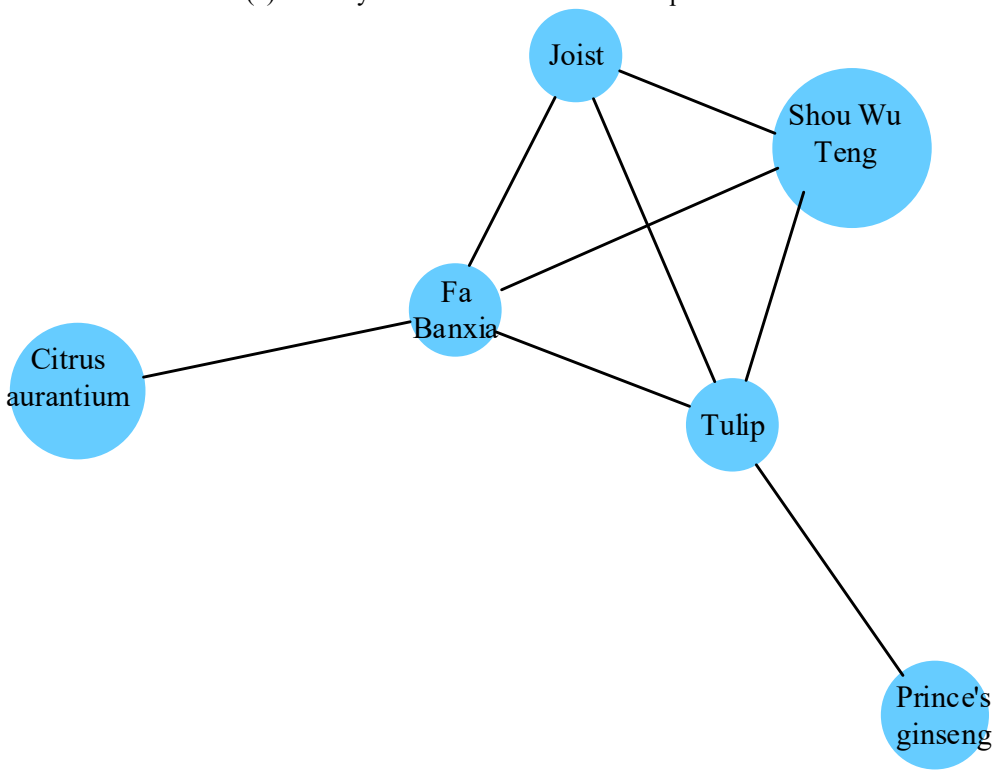
Cluster analysis

Cluster analysis of symptom systems

For the present study of systematic clustering of symptoms, the first 18 symptoms with frequency of symptom occurrence were selected and systematic clustering of Euclidean distance was carried out by the longest distance method. Fig. 4 shows the systematic clustering of symptoms. It was divided into six types with clusters of 1, 3, 2, 2, 3 and 7. Type 1 showed difficulty in falling asleep, type 2 showed sour belching, nocturnal enuresis and dizziness and type 3 showed insomnia and shorter effective sleep duration. Type 4 was dry mouth and tinnitus, type 5 was easy to wake up during sleep, difficult to fall asleep after waking up and dreaming a lot and type 6 was constipation, cold limbs, coldness, headache, bitter taste in the mouth, palpitation and chest distension. In response to the results of symptom clustering, medications can be used to target and regulate the relevant immune mechanisms to improve insomnia.



(a) First layer of Chinese medicine composition



(b) Second layer of Chinese medicine composition

Fig. 6: Complex network analysis results

Cluster analysis of drug systems

In the present study, we selected the Dan medicines in Kong Sheng Pillow and cluster analyzed the top 20 Chinese medicines in their frequency distribution, combined with the longest distance method and the Euclidean distance for the cluster analysis and the drug system aggregation is shown in Fig. 5. There are four cluster classes with cluster numbers of 7, 3, 5 and 5. The highest cluster values are for the core medicines, including Huanglian, Calamus, Cinnamon, Poria, Mother of Pearl, Shoujiao Vine and Longbiao. The second cluster consisted of Fahanxia, Yuanzhi and Yujin, while the third and fourth clusters consisted of Succinum, Sedum, Radix et Rhizoma Ginseng, Acacia, Citrus aurantium, as well as Angelica dahurica, Ligusticum Chuanxiong, Rhodiola rosea, Rhizoma Dioscorea and Cynanchum. Based on the results of drug system clustering, different regulation mechanisms can be adopted for chronic insomnia patients with different symptoms.

Complex network analysis

In this study, the Kong Sheng Pillow Zhongdan was introduced and the complex network module of the Ancient and Modern Medical Case Cloud Platform was utilized for in-depth analysis. In the setting of the complex network module, the hierarchical network algorithm relationship was carefully selected, the layout was random style and the edge weight was accurately determined to be 5 and the number of displayed edges was set to be 200. In addition, according to the actual observation needs, the node size, shape, color, font size and the edge width size, color, shape and other parameters were adjusted flexibly and meticulously in an attempt to make the network visualization effect reach the optimal state, so that the potential complex relationships and related information among TCMs can be revealed more accurately. In addition, the node size, font color, edge width, color, shape and other parameters are flexibly and carefully adjusted according to the actual observation requirements, so as to optimize the network visualization effect and to more accurately reveal the potentially complex relationships and related information among TCMs. The results of the complex network analysis are shown in Fig. 6. Fig. 6(a) shows the composition of the first layer, which consists of calamus, cinnamon, cinnamon, Huanglian, Poria, mother-of-pearl and Yuanzhi, which have the effect of sleep regulation. Figure 6(b) shows the second layer of composition of traditional Chinese medicine, which is Shouwu Teng, Longzhi, Yu Jin, Fahan Xia, Taizi Shen, Hovenia Citriodora, which is in line with the results of the screening of the active ingredients of Longzhi target and it can play the role of treating insomnia.

DISCUSSION

Health education interventions for chronic insomnia

Chronic insomnia, characterized by persistent sleep disturbances despite the absence of identifiable causes or after the resolution of underlying issues, significantly impacts individuals' health and quality of life. Effective management of chronic insomnia requires a multifaceted approach, starting with sleep hygiene education and extending to optimizing the sleep environment and medication use. Beyond pharmacological interventions, establishing a scientifically sound and correct sleep pattern is fundamental to comprehensive care for insomnia patients. This involves arranging a reasonable sleep schedule, adopting proper sleep postures, improving sleep efficiency and developing good sleep habits. Most chronic insomnia patients exhibit varying degrees of poor sleep habits, which contribute to the onset and persistence of their condition. Health education aims to make patients aware of the detrimental effects of these habits and to identify and address the underlying causes, thereby fostering the establishment of healthy sleep practices. Specifically, this includes: (1) Maintaining a regular work and rest schedule that aligns with the body's natural circadian rhythms, going to bed when sleepy and engaging in appropriate eating and drinking habits before bedtime. (2) Avoiding stimulants such as caffeine and nicotine, as well as excessive fluid intake close to bedtime. (3) Refraining from engaging in stimulating activities or vigorous exercise before bed and avoiding activities such as reading or watching intense movies or TV shows that may hinder the relaxation necessary for sleep.

Psychobehavioral and cognitive interventions for insomnia

Chronic insomnia is not merely a physiological dysfunction but often involves psychological and cognitive components. Effective holistic care requires addressing both the physiological and psychological aspects of the condition. The primary goal is to alter patients' beliefs and attitudes towards sleep, enhance their self-efficacy in managing sleep and ultimately improve insomnia symptoms. This is achieved through a comprehensive analysis of the factors contributing to insomnia, guided by professional psychotherapists. Key strategies include: (1) Educating patients about healthy sleep hygiene practices to establish reasonable sleep concepts. (2) Modifying non-adaptive sleep behaviors and reducing autonomic and cognitive arousal that may interfere with sleep. (3) Addressing attributional biases where patients may incorrectly attribute their insomnia to external factors or unknown diseases. A comprehensive and systematic etiological analysis, combined with scientifically grounded psychological and behavioral interventions, can fundamentally change patients' negative beliefs and attitudes towards sleep, thereby enhancing the effectiveness of the intervention.

Jin *et al*. (2021) highlighted that psycho-behavioral interventions and pharmacological treatments are widely accepted for chronic insomnia. However, due to the limited

availability of psycho-behavioral skills in insomnia treatment, pharmacological treatments such as antihistamines, melatonin, antidepressants and antipsychotics are often the first-line therapeutic options. Their study constructed network interaction diagrams of 61 key components corresponding to 65 major anti-insomnia targets and confirmed through molecular docking that active compounds could effectively counteract these insomnia targets. Liu *et al*. (2022) used Astragaloside B and Astragaloside E (purity ≥98%) as references and employed UPLC-Q-TOF-MS/MS to determine the chemical composition of CWT46. This method enabled the determination of neurotransmitter levels (5-HT, GABA, DA and NE) in the brain, demonstrating its efficacy in treating insomnia. Wang *et al*. (2023) investigated the hypnotic and sleep-regulating effects of Sishenwan, a traditional Chinese medicine, using cyber-pharmacology and real-time continuous monitoring of data (e.g., electrocardiograms) via wireless telemetry. Their results elucidated the molecular functions, cellular components and functional pathways involved in Sishenwan's mechanisms of action for insomnia regulation and identified key targets. Pan *et al*. (2023) explored the active ingredients and mechanisms of Jiao Tai Wan for primary insomnia treatment based on gene expression. They identified 112 potential targets for primary insomnia and confirmed through molecular docking that core compounds (e.g., quercetin, EGCG, kaempferol) have clinical applications in treating primary insomnia. Wang *et al*. (2023) applied network pharmacology and molecular docking to screen active ingredients and targets of traditional Chinese medicines like sour jujube seed and Sichuan dome. They found that activating PI3K and Akt protein expression inhibits neuronal cell apoptosis caused by sleep deprivation, thereby enhancing sleep. Deng *et al*. (2022) identified chemical components in four traditional Chinese medicines using TCMSP and PharmMapper platforms and predicted their potential targets using bioinformatics tools. They constructed a drug-target-disease network and found that these medicines exert pharmacological effects (sedation, tranquilization, antidepressant) on insomnia by acting on multiple targets in the nervous and endocrine systems. Liu *et al*. (2024) combined data mining, network pharmacology and molecular docking to identify high-frequency used TCMs and core prescriptions for insomnia treatment. They predicted effective active ingredients and targets using TCM systemic pharmacology and UniProt databases, providing a scientific basis for Chinese medicine application in insomnia treatment. Zhang *et al*. (2023) investigated the targets and mechanisms of BS in insomnia treatment using network pharmacology and molecular docking. They identified eight activities corresponding to 26 target genes related to insomnia treatment, which bind to targets involved in neurotransmitter transmission and inflammatory response modulation, exerting therapeutic effects. Xue *et al*. (2023) conducted a network meta-analysis of controlled trials published before October 31, 2022 and found that Suvorexant (20 mg and 40 mg) and Daridorexant (10 mg and 50 mg) are most effective in reducing sleep latency. Lemborexant (5 mg and 10 mg) was most effective in reducing subjective time to sleep and perceived time awake during the night, showing overall efficacy in insomnia treatment. Wang *et al*. (2024) studied the effects of composite jujube nut granules on insomnia in rats with CUMS-PCPA. The granules improved sleep quality by regulating neurotransmitter balance, inhibiting inflammatory responses and modulating the cAMP/CREB signaling pathway, ultimately improving insomnia symptoms. Ren *et al*. (2023) evaluated the sleep-improving effects of a mixture of jujube kernel and γ-aminobutyric acid (ZSSG) in mice. ZSSG significantly improved sleep quality, reduced sleep onset time and prolonged sleep duration in a sodium pentobarbital-induced sleep model, with increased brain GABA levels.

CONCLUSION

This study, grounded in network pharmacology, explores the potential mechanisms of Kong Sheng Pillow Zhongdan in treating chronic insomnia. We constructed a comprehensive drug-ingredient-target-disease network, identifying 126 intersecting genes between the core prescription and insomnia targets. This overlap underscores the complexity of insomnia treatment, highlighting the multifaceted nature of drug-target interactions. Our findings suggest that Kong Sheng Pillow Zhongdan may exert its therapeutic effects by modulating neurotransmitter transmission and inflammatory responses, potentially through active ingredients like kaempferol targeting RELA.

Complex network analysis further revealed that herbs such as calamus, cinnamon, rhizoma coptidis, Poria, mother-of-pearl and Yuanzhi have sleep-regulating effects. Additionally, herbs like shouwu teng, longan, yujin, fazhanxia, tai zi ginseng and citrus aurantium, which align with the active ingredients identified in longan target points, play a significant role in insomnia treatment. These findings provide a scientific basis for the traditional use of these herbs in managing insomnia.

For chronic insomnia patients, our study underscores the importance of integrating health education and psycho-behavioral cognitive interventions. These strategies aim to address the underlying factors contributing to insomnia and promote the establishment of healthy sleep habits, ultimately reducing insomnia symptoms. Future research should focus on experimental validation of these findings and exploring the clinical applications of Kong Sheng Pillow Zhongdan. This work not only contributes to the understanding of chronic insomnia's neuroimmune mechanisms but also highlights the potential of traditional Chinese medicine in developing novel therapeutic approaches.

Acknowledgments
Not applicable.

Authors' contributions
Yun Lu investigation, resources, supervision, funding acquisition, writing – review & editing. All authors read and approved the final manuscript.

Funding
No external funding was received.

Data availability statement
All data generated or analysed during this study are included in this published article and its supplementary information files.

Ethical approval
This network-pharmacology study used exclusively public, de-identified databases; no human or animal subjects were involved. Ethical approval was therefore not required (approval number: N/A).

Conflict of interest
The authors declare no competing financial or non-financial interests.

REFERENCES

Barshir R, Fishilevich S, Iny-Stein T, Zelig O and Lancet D (2021). Genecarna: A comprehensive gene-centric database of human non-coding rnas in the genecards suite. *J. Mol. Biol.* **433**: 166913.

Belanger HG, Lee C and Winsberg M (2023). Symptom clustering of major depression in a national telehealth sample. *J. Affect. Disord.* **338**: 129-134.

Deng Q, Huang L, Yu F, Lin J, Hu L, Zhao J and Wu S (2022). Biomedical analytics of four chinese medicinals in treatment of insomnia based on network pharmacology. *BioMed Res. Int.* 2022: 9414262.

Dressle RJ, Feige B, Spiegelhalder K, Schmucker C, Benz F, Mey NC and Riemann D (2022). HPA axis activity in patients with chronic insomnia: A systematic review and meta-analysis of case–control studies. *Sleep Med. Rev.* **62**: 101588.

Fernandes M, Placidi F, Mercuri NB and Liguori C (2024). Daridorexant treatment for chronic insomnia: A real-world retrospective single-center study. *Neurol. Sci.* **45**(7): 3443-3448.

Gao X, Li J, Xu SP, Li XY, Wang X and Li Y (2023). Oral nicotinamide mononucleotide (nmn) to treat chronic insomnia: Protocol for the multicenter, randomized, double-blinded, placebo-controlled trial. *Trials* **24**: 234.

He JK, Jia BH, Wang Y, Li SY, Zhao B and Zhou ZG (2022). Transcutaneous auricular vagus nerve stimulation modulates the prefrontal cortex in chronic insomnia patients: FMRI study in the first session. *Front. Neurol.* **13**: 555.

Jin D, Zhang J, Zhang Y, An X, Zhao S, Duan L and Tong X (2021). Network pharmacology-based and molecular docking prediction of the active ingredients and mechanism of ZaoRenDiHuang capsules for application in insomnia treatment. *Comput. Biol. Med.* **135**: 104562.

Liu H, Yang L, Wan C, Li Z, Yan G, Han Y and Wang X (2022). Exploring potential mechanism of ciwujia tablets for insomnia by UPLC-Q-TOF-MS/MS, network pharmacology and experimental validation. *Front. Pharmacol.* **13**: 990996.

Liu X, Sun P, Bao X, Cao Y, Wang L and Wang Q (2024). Potential mechanisms of traditional chinese medicine in treating insomnia: A network pharmacology, geo validation and molecular-docking study. *Medicine* **103**(18): e38052.

Martinez C, Kato MM and Currier M (2024). Improving sleep outcomes in patients with cancer with chronic insomnia using cognitive behavioral therapy: A retrospective study. *J. Clin. Oncol.* **42**(16 supply): e13555-e13555.

Mittal H, Rawat VS, Tripathi R and Gupta R (2024). Cognitive functioning in adults with chronic insomnia disorder- a cross-sectional study. *Indian J. Psychiatry* **66**(9): 846-852.

Othman A, Tashkandi A, Esilan H, Alfeheadi GM and Alqusair S (2023). Assessment of insomnia among emergency department physicians in the western region of saudi arabia, 2023. *Cureus* **15**: e45678.

Palagini L, Geoffroy PA, Alfi G, Annuzzi E, Gurrieri R and Caruso V (2024). Insomnia and the orexinergic pathway in the link with psychopathology: Effects of doras in insomnia comorbid with mental disturbances. *Curr. Sleep Med. Rep.,* **10**: 119-131.

Palagini L, Geoffroy PA, Alfi G, Annuzzi E, Gurrieri R and Caruso V (2024). Insomnia and the orexinergic pathway in the link with psychopathology: Effects of doras in insomnia comorbid with mental disturbances. *Curr. Sleep Med. Rep.* **10**: 119-131.

Pan L, Wang Y, Guan R and Shi Q (2023). Study on the active ingredients and mechanism of Jiaotai Pill in the treatment of primary insomnia based on network pharmacology and GEO statistics: A review. *Medicine* **102**(38): e35253.

Ren A, Wu T, Wang Y, Fan Q, Yang Z and Zhang S (2023). Integrating animal experiments, mass spectrometry and network-based approach to reveal the sleep-improving effects of ziziphi spinosae semen and γ-aminobutyric acid mixture. *Chin. Med.* **18**: 45.

Selsick H, Heidbreder A, Ellis J, Ferini-Strambi L, García-Borreguero D and Leontiou C (2024). Assessment and management of chronic insomnia disorder: An algorithm for primary care physicians. *BMC Prim. Care* **25**: 123.

Shuai J (2023). The pathogenesis and intervention of sleep disorders. *Front. Neurosci.* **17**: 1176932.

Wang LX, Zhao Q, Zhang Y, Xue R, Li S, Li Y and Zhang YZ (2023). Network pharmacology and

pharmacological evaluation for deciphering novel indication of Sishen Wan in insomnia treatment. *Phytomedicine* **108**: 154500.

Wang S, Zhao Y and Hu X (2023). Exploring the mechanism of Suanzaoren decoction in treatment of insomnia based on network pharmacology and molecular docking. *Front. Pharmacol.,* **14**: 1145532.

Wang Z, Li D, Chen M, Yu X, Chen C and Chen Y (2024). A comprehensive study on the regulation of compound zaoren granules on camp/creb signaling pathway and metabolic disorder in cums-pcpa induced insomnia rats. *J. Ethnopharmacol.,* **332**: 117892.

Xue T, Wu X, Li J, Chen S, Wang Z and Tan X (2023). Different doses of dual orexin receptor antagonists in primary insomnia: A bayesian network analysis. *Front. Pharmacol.* **14**: 112233.

Yang B and Liu H (2020). Automatic identification of insomnia based on single-channel eeg labelled with sleep stage annotations. *IEEE Access,* **8**: 22345-22356.

Zhang Y, Sun Q, Li H, Wang D, Wang Y and Wang Z (2023). Lower serum insulin-like growth factor 1 concentrations in patients with chronic insomnia disorder. *Front. Psychiatry* **14**: 987654.

Zhang Y, Zhang Z, Wang S, Yang JN, Zhao ZM and Liu X (2023). Molecular targets and mechanisms involved in the action of banxia shumi decoction in insomnia treatment. *Medicine* **102**: e12345.

Zhao X, Hou T, Zhou H, Liu Z, Liu Y and Wang C (2023). Multi-effective components and their target mechanism of *Ziziphi spinosae* semen in the treatment of insomnia. *Fitoterapia.,* **171**: 105523.