Screening of Effective Traditional Chinese Medicine Monomer Compounds for the Treatment of Nonorganic Sleep Disorders Based on Network Pharmacology

Conghui WANG[1], Xiong CHEN[1], Keke MA[2], Jiale LIAO[2], Chunqi AI[1]*

1. Mental Health Center, Taihe Hospital, Hubei University of Medicine, Shiyan 442000, China; 2. Graduate School, Hubei University of Medicine, Shiyan 442000, China

Abstract [**Objectives**] To find effective monomer compounds of traditional Chinese medicine targeting nonorganic sleep disorders. [**Methods**] The reverse thinking of "target-compound" was adopted to search for effective traditional Chinese medicine monomer compounds that intervene in the core targets of nonorganic sleep disorders, and molecular docking technology was used to verify the traditional Chinese medicine monomer compounds that meet the expected goals. [**Results**] Based on the storm related targets of nonorganic sleep disorders, five monomer compounds of traditional Chinese medicine were screened, namely paeoniflorin, chlorogenic acid, quercetin, baicalin, and ginsenoside Rg1. These monomer compounds of traditional Chinese medicine act on multiple targets such as CASP8, IKBKB, IL1B, IL6, CXCL8, *etc.*, thereby playing a role in calming the mind and improving sleep. [**Conclusions**] These monomer compounds of traditional Chinese medicine had potential pharmacological effects on nonorganic sleep disorders and high value in subsequent experiments and clinical applications.

Key words Nonorganic sleep disorders, Monomer compounds of traditional Chinese medicine, Target, Network pharmacology

1 Introduction

Nonorganic sleep disorders are a condition of unsatisfactory sleep quality primarily characterized by insomnia, with other symptoms secondary to insomnia, including difficult falling asleep, shallow sleep, easy awakening, frequent dreaming, early awakening, difficult falling back asleep after waking up, discomfort during waking up, fatigue, or daytime drowsiness. Insomnia can cause anxiety, depression, or fear in patients, leading to a decrease in mental activity efficiency and hindering social function[1]. Under the guidance of both traditional Chinese and Western medicine, a large number of traditional Chinese patent medicines and simple preparations and traditional Chinese medicine prescriptions recommended in the diagnosis and treatment plans issued and repeatedly revised by the China's National Health Commission and the State Administration of Traditional Chinese Medicine have demonstrated good clinical therapeutic effects[2]. This paper adopted the reverse thinking of "target-compound" to search for effective traditional Chinese medicine monomer compounds that intervene in the core targets of nonorganic sleep disorders, and used molecular docking technology to verify the reliability of traditional Chinese medicine monomer compounds that meet the expected goals. This could provide new ideas for the development of drugs for the treatment of nonorganic sleep disorders and reliable simulation data for the next basic experiments.

2 Methods

The keywords "non-organic sleep disorder" and "inflammatory storm" were used to search the targets related to nonorganic sleep disorders and inflammatory storms in GeneCards database. The targets searched from two keywords were saved as two independent lists and exported for subsequent analysis. Intersection targets were screened by using R language (version: 4.1.0) and VennDiagram program package, and the lists of targets for nonorganic sleep disorders and inflammatory storms were imported into R. By drawing a Venn diagram, the intersection targets of the two were obtained and visualized. Compounds that meet the criteria were sorted by degree value, and the top 5 candidate traditional Chinese medicine monomer compounds were selected. Molecular docking was to download three-dimensional structures related to core target proteins of nonorganic sleep disorders, such as ACE2 receptor (PDB: 1R42) and 3CLpro (PDB ID: 6LU7).

3 Results and analysis

3.1 Screening targets for nonorganic sleep disorder storms

A total of 767 targets for sleep disorder and 469 targets for inflammatory storm were retrieved from the Genecards database. These targets were imported into R language, and the "VennDiagram" program package was used to intersect the targets of nonorganic sleep disorders, resulting in a total of 275 common targets, as shown in Fig. 1.

3.2 GO and KEGG analysis of nonorganic sleep disorder targets The gene ontology (GO) entries included 1 076 biological processes (BP), 16 cellular components (CC), and 48 molecular functions (MF). Based on Count (Gene in GO and hit list, the number of genes involved in the biological process, cell composition, or molecular function) and FDR [log (*q*-value), the corrected *P*-value], the analysis results of BP, CC, and MF were sorted. Among them, the higher the Count value, the more meaningful it is, and the smaller the FDR value, the more meaningful it is.

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* Corresponding author. E-mail: 465488293@qq.com

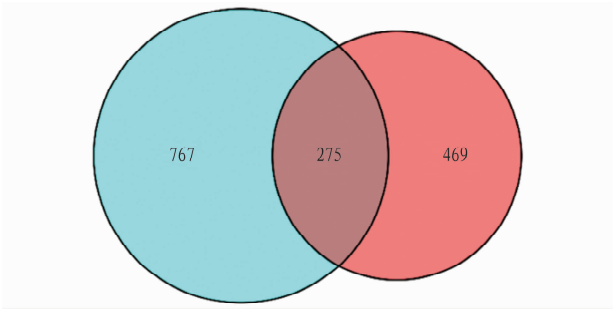

Fig. 1 Nonorganic sleep disorder targets

3.3 PPI network topology analysis of nonorganic sleep disorder targets The targets of nonorganic sleep disorders were imported and uploaded to the Sring database. Limiting the species as "Homo sapiens", a file of the interaction relationships among 275 target genes of nonorganic sleep disorders was obtained, and then it was input into Cytoscape. Through the CytoNCA plug-in of this software, the PPI network was analyzed and calculated, and targets were screened based on their Betweenness, Closeness, Degree, Eigenvector, LAC, and Network values. After 3 rounds of screening, 34 core targets were finally obtained, and they were IFNA1, TRAF6, IKBKB, STAT1, CCL5, CASP8, ALB, CD4, CCL2, IFNG, IL1B, TP53, EGFR, HIF1A, TLR4, JUN, CXCL8, IL10, VEGFA, IL6, TNF, INS, NFKB1, TLR2, IL18, IRF1, HMGB1, IRF3, RELA, STAT3, IL2, IL4, CSF2, and IL17A (Fig. 2).

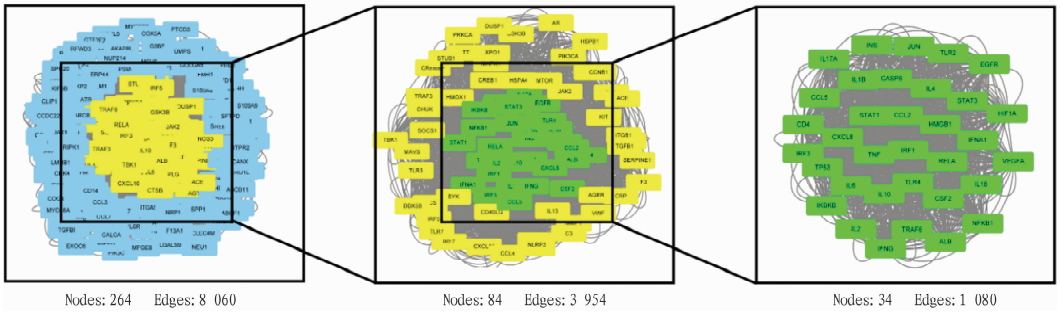

Fig. 2 PPI network topology analysis

3.4 Molecular docking verification After processing the target protein files and traditional Chinese medicine monomer compound files using Pymol and AutoDockTools, molecular docking was performed using Vina software. Through docking results, it was found that MOL000098, MOL006821, MOL000006, MOL003187, and MOL013179 had good binding activity with their corresponding core targets, ACE2 receptors, and 3CLpro of nonorganic sleep disorders, indicating that the above components had great potential for intervening in nonorganic sleep disorders.

3.5 Joint analysis of candidate traditional Chinese medicine monomer compounds and important pathways of KEGG enrichment 20 nonorganic sleep disorder core targets related to 5 candidate traditional Chinese medicine monomer compounds (MOL000098, MOL006821, MOL000006, MOL003187, and MOL013179) were imported into R language. Finally, five meaningful traditional Chinese medicine monomer compounds were obtained, which had more core targets acting on nonorganic sleep disorders, namely paeoniflorin, chlorogenic acid, quercetin, baicalin, and ginsenoside Rg1 (Fig. 3).

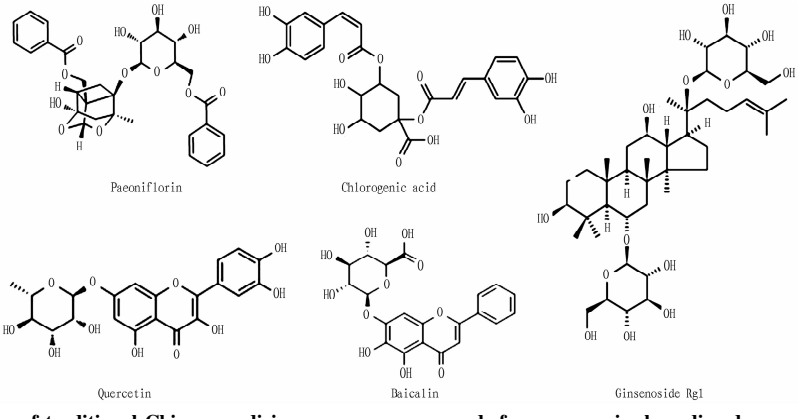

Fig. 3 Structural formulas of traditional Chinese medicine monomer compounds for nonorganic sleep disorders

4 Discussion

After data analysis, a detailed description of these five traditional Chinese medicine monomer compounds was provided, including their sources, chemical structures, pharmacological mechanisms, research progress related to nonorganic sleep disorders, and potential clinical application value. Paeoniflorin is a main component of *Paeonia lactiflora* Pall., a plant in Paeoniaceae, and belongs to the monoterpenoid glycosides. Its chemical name is 3,4,5-trihy-

droxy-2-methylbenzoic acid 1-O-β-D-glucopyranoside. Paeoniflorin is widely used in traditional Chinese medicine formulas, especially in the treatment of pain, inflammation, and neurological diseases, with significant effects[3]. Paeoniflorin has various pharmacological activities, including anti-inflammatory, antioxidant, sedative, and neurotransmitter regulating effects. Its calming effects mainly improve sleep quality by regulating the levels of neurotransmitters such as γ-aminobutyric acid (GABA) and serotonin (5-HT) in the central nervous system. Combining modern pharmacological research, paeoniflorin is expected to become an important candidate ingredient for the development of new treatment drugs for sleep disorder. Chlorogenic acid is a phenolic compound widely present in plants, especially abundant in coffee, green tea, *Crataegus pinnatifida* and other plants. Its chemical structure is 3-(3,4-dihydroxybutyric acid) ethyl acetate, which belongs to ester compounds. Chlorogenic acid has attracted much attention due to its excellent antioxidant and anti-inflammatory properties. Chlorogenic acid has significant antioxidant and anti-inflammatory effects, and protected nerve cells from damage by clearing free radicals and inhibiting oxidative stress response[4]. In addition, chlorogenic acid can regulate the metabolism of neurotransmitters, especially GABA and 5-HT levels, thereby improving sleep quality. By regulating the levels of oxidative stress and inflammatory response in the brain, chlorogenic acid can significantly prolong the total sleep time of mice and reduce the latency to sleep. Quercetin is a flavonoid compound widely present in fruits, vegetables, and tea, particularly abundant in apples, onions, berries, and green tea[5]. Its chemical structure is 3, 3', 4', 5, 7-pentahydroxyflavone, which has the structural characteristics of multiple hydroxyl groups, endowing it with excellent antioxidant properties. Quercetin can regulate the balance of neurotransmitters, especially promoting sleep by modulating the GABA and 5-HT systems. In addition, quercetin can also inhibit the release of inflammatory factors and alleviate the inflammatory response of the nervous system. Quercetin has shown potential to improve sleep quality in multiple studies. Animal experiments have shown that quercetin can significantly prolong the total sleep time of mice, shorten the latency period to sleep, and improve sleep efficiency[6-7]. Baicalin is the main active ingredient in *Scutellaria baicalensis* Georgi and belongs to the flavonoids. Baicalin promotes the occurrence and maintenance of sleep by regulating the metabolism of neurotransmitters, especially GABA and 5-HT. In addition, baicalin can alleviate stress responses and further improve sleep quality by regulating the function of the HPA axis. Ginsenoside Rg1 is a main component in *Panax ginseng* C. A. Mey. and belongs to the ginsenoside compounds. Its chemical structure is diterpenoid saponin, with a complex glycosidic bond structure, which gives it good biological activity and pharmacological effects. Ginsenoside Rg1 has various pharmacological activities, including neuroprotective, antioxidant, anti-inflammatory, and neurotransmitter regulating effects. Rg1 can promote the survival and repair of nerve cells by regulating signaling pathways within the cells, such as the PI3K/Akt and MAPK pathways. In addition, Rg1 can regulate the function of the central nervous system and promote the occurrence and maintenance of sleep by increasing the levels of GABA and 5-HT. Rg1 can also alleviate stress responses and further improve nonorganic sleep disorders caused by stress by regulating the function of the HPA axis. Ginsenoside Rg1, as a natural active ingredient, has good safety and multiple pharmacological effects, making it widely applicable in clinical practice.

In summary, the five monomer compounds of traditional Chinese medicine, namely paeoniflorin, chlorogenic acid, quercetin, baicalin, and ginsenoside Rg1, exhibit strong potential in regulating core targets related to nonorganic sleep disorders. They act on sleep regulation and emotional stability through multiple mechanisms, including regulating neurotransmitter balance, antioxidant, anti-inflammatory, and HPA axis function. In addition, these compounds have good safety and tolerability, are suitable for long-term use, and have broad clinical application prospects. Future research should further explore the specific application effects of these traditional Chinese medicine monomer compounds in clinical practice, optimize their dosage and administration methods, and combine modern pharmacological techniques to deeply analyze their molecular mechanisms. Furthermore, by combining network pharmacology and molecular docking technology, more potential monomer compounds of traditional Chinese medicine can be screened and validated, providing richer and more effective options for the treatment of nonorganic sleep disorders[8]. Through the systematic screening and validation of this paper, these five monomer compounds of traditional Chinese medicine not only provided new ideas and directions for the treatment of nonorganic sleep disorders, but also laid a solid foundation for the modernization and international application of traditional Chinese medicine. In the future, these compounds are expected to play a greater role in clinical practice with research depth, improving patients' sleep quality and enhancing their quality of life.

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