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Exploring the Molecular Mechanism of the Memie Formula in the Treatment of Insomnia Based on Network Pharmacology and Molecular Docking Technology

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Abstract: *To elucidate the underlying mechanisms of the "Memie Anshen Formula" in treating insomnia, this study leveraged databases including TCMSP, HERB, ETCM, and STITCH to pinpoint the active constituents of the remedy and their potential targets. Insomnia-related target data were collated from OMIM, GeneCards, and DrugBank. Interactions between target proteins were ascertained via the String database, leading to the construction of a protein-protein interaction network in Cytoscape. The research involved GO function and KEGG pathway enrichment analyses executed with R language and its suite of bioinformatics tools, complemented by molecular docking for empirical validation. The analysis identified 67 active ingredients and 87 intersection targets pertinent to insomnia. Molecular docking affirmed effective affinities between the formula's active components and the targets. Enrichment analyses highlighted the GABA signaling and serotonin signaling pathways, indicating the formula's anti-insomnia effects may be mediated through targets such as CYP1B1, ESR1, ABCB1, and HTR2A.*

Keywords: *Traditional Chinese Medicine Compound Network Pharmacology, Insomnia, Memie, Traditional Chinese Medicine, Chinese Medicine*

1. Introduction

Insomnia is when someone struggles to fall asleep despite having the chance to do so, which can adversely affect their daytime activities, including work. This condition is widespread, affecting between 19% and 50% of adults according to various studies[1]. Among patients visiting primary healthcare institutions, up to 20% of patients report symptoms of insomnia, which can lead to functional impairment and decreased productivity. Additionally, in the United States, the direct and indirect costs associated with insomnia amount to approximately 100 billion dollars[2]. If not addressed, insomnia can lead to an increased risk of both heart disease and mental health problems[3].

The underlying causes of insomnia remain largely unknown. Treatment options beyond medication include a variety of methods such as cognitive behavioral therapy, music therapy, physical exercise, transcranial magnetic stimulation, meditation, acupuncture, cupping, and acupressure, which can all help enhance sleep quality and reduce anxiety levels[4-6]. The World Sleep Society endorses cognitive behavioral therapy as the top treatment choice for chronic insomnia, though its accessibility is hindered by high costs and a lack of medical resources. As for medication, treatments range from barbiturates and benzodiazepines to melatonin receptor agonists and antidepressants, among others. Despite their efficacy, these drugs can come with unwanted side effects like dependency, cognitive issues, falls, and withdrawal complications[2, 7, 8].

In recent years, with the development of scientific research methods, researchers have begun to delve into the molecular mechanisms of traditional Chinese medicine (TCM) in treating insomnia through modern scientific technologies such as network pharmacology. "Network pharmacology" was first proposed by Hopkins at the University of Dundee in the UK[9]. It is based on the theories of systems

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biology and polypharmacology and is called the new paradigm of the next generation of drug research. It has been widely applied in the research of TCM syndromes, the theory of TCM formula compatibility, pharmacology of Chinese herbal medicine, and new drug discovery. The theory of TCM emphasizes a holistic view, which is quite similar to the systemic nature of network pharmacology. The concepts of network pharmacology, such as multiple targets, multiple pathways, and forming a network, have unique advantages in studying the compatibility and mechanism of action of TCM compound formulas. As a new paradigm, integrating it into the theoretical research of TCM can better explain the molecular mechanisms of TCM[10].

2. Information and Methods

2.1. Identifying Active Ingredients and Their Target Genes

For the "Memie Anshen Formula" (including herbs Pinellia, Albizia julibrissin, Polygonum cuspidatum, Juncus effusus, Ziziphus jujuba, Tortoise shell, Artemisia argyi, Lavender, Rose, and Agastache rugosa), a detailed analysis of their chemical components was conducted using three key databases: the TCMSP (Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform, https://old.tcmsp-e.com/tcmsp.php), the ETCM (Encyclopedia of Traditional Chinese Medicine, http://www.tcmip.cn/ETCM/), and the HERB (Chinese Herbal Medicine Database, http://herb.ac.cn/). Components were selected based on their Oral Bioavailability (OB) of at least 30% and Drug-Likeness (DL) of at least 0.18 in the TCMSP database, and a "medium to good" rating for drug similarity in the ETCM database. Their chemical structures, identified through their PubChem IDs, were further analyzed using the Swiss ADME database to filter active ingredients adhering to drug-likeness principles. Target predictions for these active components were made using the Swiss Target Prediction database, with a merging and deduplication process involving targets found in the ETCM database to pinpoint the final active ingredient targets.

2.2. Selecting Disease-Related Targets

The search for targets associated with "insomnia" and "sleep disorder" was conducted through platforms such as Drug Bank, OMIM (Online Mendelian Inheritance in Man), and DisGeNET.

2.3. Identifying Common Targets between the Formula and Disease

Using the Venny 2.1 online tool, a Venn diagram was created to visualize the overlap between the formula's target genes and those associated with the disease. This intersection identifies the potential targets through which the "Memie Anshen Formula" might act in treating insomnia.

2.4. Building the Network of Potential Target Interactions

The identified overlapping targets were uploaded to the STRING database, selecting "Homo sapiens" as the species and setting the confidence threshold at 0.4. This step produced a network graph illustrating how these target proteins interact with each other. The resultant Protein-Protein Interaction (PPI) network was then saved as a "string interactions.tsv" file and imported into the Cytoscape v 3.7.2 software to map out the PPI network specifically for the treatment of insomnia using the "Memie Anshen Formula." To understand the network's structure better, we analyzed its topology within Cytoscape, focusing on key metrics like Degree Centrality (DC), Betweenness Centrality (BC), and Closeness Centrality (CC).

2.5. Functional and Pathway Enrichment Analysis of Potential Targets

Employing R language and a suite of packages ("RSQLite," "Bioc Manager," "Colorspace," "Stringi," "DOSE," "ClusterProfiler," "Pathview"), we proceeded to analyze the KEGG pathways and GO functions enriched among the targets common to both the drug and the disease. For this, we converted the intersecting targets into gene IDs. Only pathways and functions with a p-value less than 0.05 were considered significant and selected for further analysis.

2.6. Building the Interaction Network

Using Cytoscape v 3.7.2 software, we created a comprehensive network that maps out how the

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"Memie Anshen Formula" for insomnia connects its traditional Chinese medicinal components, active compounds, key targets, and relevant pathways. This network forms the basis of understanding the formula's mechanism in combating insomnia.

2.7. Docking Molecules to Proteins

For the detailed study of how the active compounds interact with specific proteins, we employed Autodock Vina 1.2.2, a tool specialized for docking small molecules into the binding sites of proteins. We sourced the molecular structures of compounds like quercetin, apigenin, and others from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). Concurrently, we acquired the 3D structures of proteins such as ESR1, ABCB1, and SLC6A4 from the PDB (Protein Data Bank, (http://www.rcsb.org/)) database. By converting all related files into PDBQT format—stripping away water molecules and adding polar hydrogen atoms—we prepared them for docking. The interactions between these molecules and proteins were then meticulously visualized using Autodock Vina 1.2.2 (http://autodock.scripps.edu/), shedding light on potential therapeutic effects of the "Memie Anshen Formula" on insomnia through molecular interactions.

3. Results

3.1. Screening Outcomes for Active Compounds and Potential Targets

After thorough examination of databases and related literature, and excluding compounds without target associations, we identified a total of 67 active compounds across various herbs in the "Memie Anshen Formula." Specifically, Artemisia argyi contributed 25 compounds, Pinellia had 9, Juncus effusus contributed 1, Tortoise shell had 2, Albizia julibrissin contributed 4, Agastache rugosa had 6, Roses added 8, Ziziphus jujuba contributed 9, and Polygonum cuspidatum added 3. After removing duplicates, we identified 405 unique targets. The table provided lists the top 10 active compounds ranked by their Degree of interaction with these targets (Table 1).

Table 1: Active ingredients.

CAS-id	Molecule Name	Molecular Formula	Degree
520-36-5	apigenin	C15H10O5	27
4666-84-6	cryptomeridiol	C15H28O2	21
6545-25-1	n-methylasimilobine	C18H19NO2	18
117-39-5	quercetin	C15H10O7	17
97-53-0	eugenol	C10H12O2	17
491-67-8	baicalein	C15H10O5	17
299-42-3	ephedrine	C10H15NO	17
1447-88-7	dinatin	C16H12O6	15
78417-26-2	5,7,3'-trihydroxy-6,4',5'-trimethoxyflavone	C18H16O8	13
56226-95-0	5,6,4'-trihydroxy-7,3'-dimethoxyflavone	C17H14O7	10

3.2. Common Targets between the Formula and Insomnia

Initially, the search across DrugBank, OMIM, and DisGeNET databases yielded 176, 140, and 226 disease targets respectively. After combining and removing duplicates from these three sources, we identified a total of 508 unique disease-related targets. Cross-referencing these with the potential targets of the active compounds led to the identification of 87 target genes shared between the treatment formula and the disease. The Venn diagram illustrates that these 87 potential targets represent 10.5% of the total number of targets identified (Figure 1), highlighting the focused action of the "Memie Anshen Formula" on specific genes associated with insomnia.

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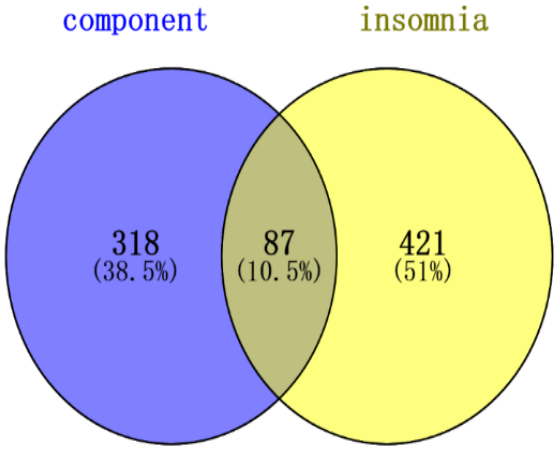
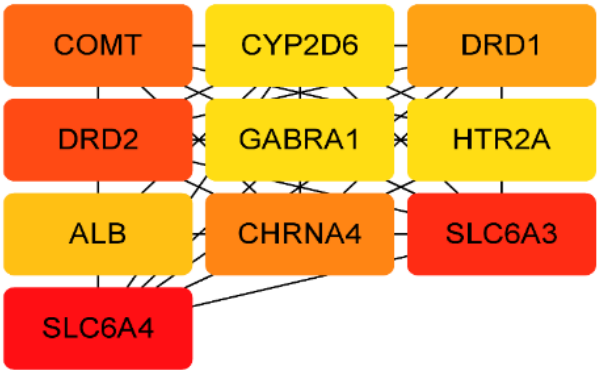


Figure 1: Target intersection veen plot.

To delve deeper into the potential mechanisms by which the formula might address insomnia, we imported the 87 intersecting targets into the STRING database to create a Protein-Protein Interaction (PPI) network (Figure 2). The PPI network was then analyzed in Cytoscape 3.7.2 software, which facilitated the selection and visualization of core nodes. By employing the CytoHubba plugin and focusing on the degree of connectivity, we identified the top 10 core genes (Figure 3), which are SLC6A4, SLC6A3, DRD2, COMT, CHRNA4, DRD1, ALB, CYP2D6, HTR2A, and GABRA1(Table 2). Analysis of the PPI network highlighted that the γ-aminobutyric acid (GABA) subunits are among the most significant genes involved. This insight suggests that the formula's impact on insomnia might be largely mediated through pathways involving these GABAergic genes.

Figure 2: PPI network diagram.



Note: The redder the color, the greater the degree value.

Figure 3: Core Genes.

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Table 2: Degree value of the top 10 targets.

Rank	Betweenness Centrality	Closeness Centrality	Clustering Coefficient	Degree	name
1	0.08287746	0.625	0.3033033	37	SLC6A4
2	0.07783263	0.61594203	0.28412698	36	SLC6A3
3	0.07415762	0.61594203	0.35798319	35	DRD2
4	0.06285504	0.59440559	0.33978495	31	COMT
5	0.03060319	0.56291391	0.42298851	30	CHRNA4
6	0.03122609	0.55555556	0.40640394	29	DRD1
7	0.06736901	0.55194805	0.31216931	28	ALB
8	0.04921735	0.5704698	0.35612536	27	CYP2D6
9	0.03475984	0.55921053	0.41025641	27	HTR2A
10	0.04455225	0.5483871	0.54415954	27	GABRA1

3.3. KEGG Pathway and GO Functional Enrichment Analysis

The analysis resulted in identifying 857 biological processes, 63 cellular components, 153 molecular functions, and 19 signaling pathways. Figure 4 shows a bar graph representing the GO functional enrichment analysis. The horizontal axis categorizes the types of enriched functions that the proteins are involved in, while the vertical axis indicates the number of target genes enriched in each functional category.

Figure 5 presents a bubble chart for the KEGG pathway enrichment analysis. Here, the vertical axis displays the enriched information of the gene intersections in various KEGG pathways, while the horizontal axis shows the proportion of gene intersections in specific KEGG pathways, denoted as the GeneRatio. The size of each bubble indicates the number of intersecting genes enriched in a KEGG pathway, represented by the Count value. The Q-value, a corrected form of the P-value ranging from 0 to 1, is visualized through the color gradient of the bubbles, with a shift towards yellow indicating higher levels of enrichment.

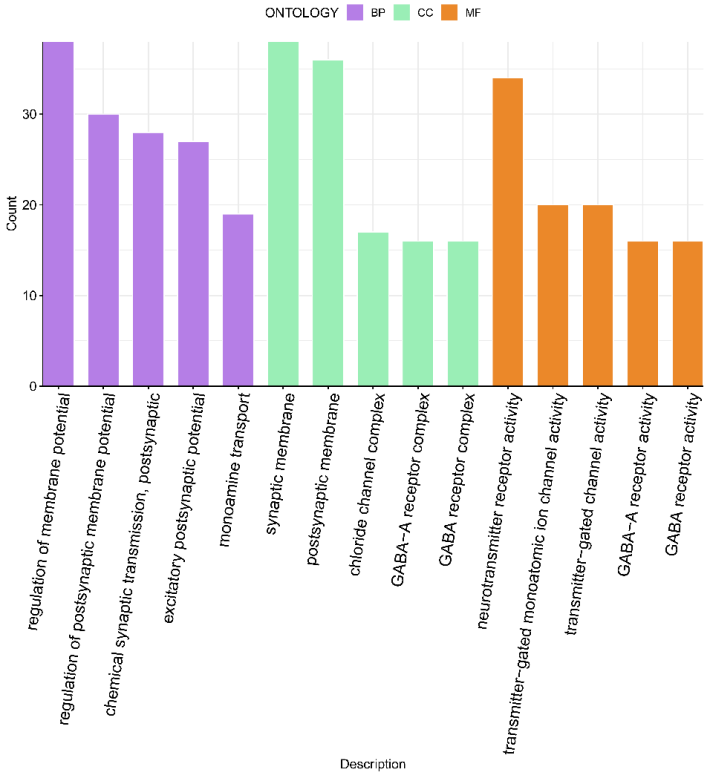

Figure 4: GO function enrichment bar chart.

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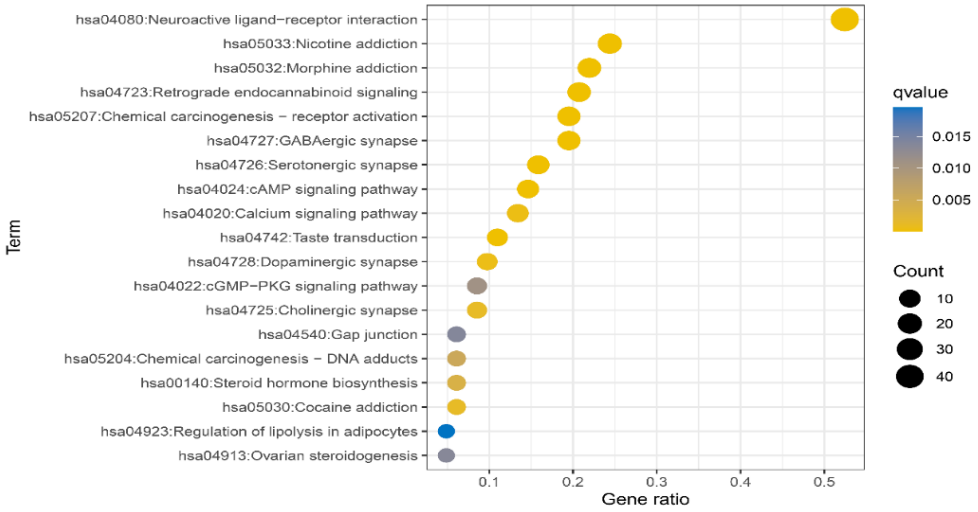
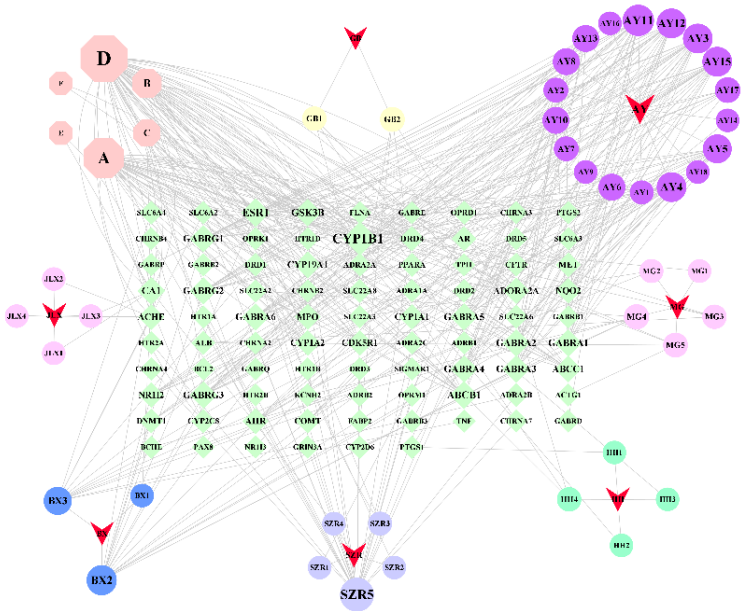


Figure 5: Enrichment analysis of KEGG pathway.

3.4. Molecular Docking Analysis

Based on the PPI network and the traditional Chinese medicine-component-target diagram (Figure 6), the proteins selected for molecular docking included ESR1, ABCB1, SLC6A4, DRD2, COMT, CHRNA4, DRD1, ALB, GABRA1, HTR2A, and CYP2D6 (Table 3). The top 10 active compounds, ranked by their degree of interaction and chosen as ligands for docking, were quercetin, apigenin, n-methylasimilobine, cryptomeridiol, baicalein, 5,6-dihydroxy-7,3',4'-trimethoxyflavone, ladanein, 5,7,3'-trihydroxy-6,4',5'-trimethoxyflavone, dinatin, and luteolin (Table 4).



Note: Triangles represent traditional Chinese medicine, circles denote the components of the medicine, and diamonds refer to the intersecting genes

Figure 6: Drug-Component-Target Network Diagram.

After conducting molecular docking analysis using various databases and software tools to examine the interactions between receptor proteins and ligand molecules, we obtained binding affinity scores for these interactions, as depicted in the figures. The results showed that all the binding scores between the active components and the target proteins were negative. This indicates that the binding affinity of the key active components is very close to, with the intensity of binding affinity distinguishable by the depth of color darker colors signify stronger binding affinities[11] (Figure 7). The interactions between HTR2A and five active components were further visualized using PyMOL for a detailed analysis of the interaction forces[12], as shown in the Figure 8.

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Table 3: Core target information involved in molecular docking.

Target	PDB-ID	Resolution
ESR1	1XP1	1.80 A
ABCB1	7A69	1.78 A
SLC6A4	5I6X	3.14 A
DRD2	7JVR	2.8 A
COMT	3BWY	1.30 A
CHRNA4	8ST0	2.4 A
DRD1	7JVP	2.90 A
ALB	3SQJ	2.05 A
GABRA1	6X3T	2.55 A
HTR2A	7WC8	2.45 A
CYP2D6	3TBG	2.1 A

Table 4: Key chemical composition information involved in molecular docking.

Number	Molecule Name	Molecular Formula
S0	quercetin	C15H10O7
S1	apigenin	C15H10O5
S2	n-methylasimilobine	C18H19NO2
S3	cryptomeridiol	C15H28O2
S4	baicalein	C15H10O5
S5	5,6-dihydroxy-7,3',4'-trimethoxyflavone	C18H16O7
S6	ladanein	C17H14O6
S7	5,6,4'-trihydroxy-7,3'-dimethoxyflavone	C17H14O7
S8	dinatin	C16H12O6
S9	luteolin	C15H10O6

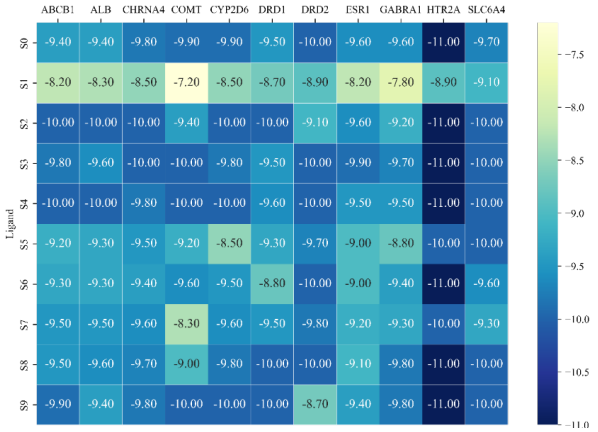

Figure 7: Molecular docking results binding energy heat map.

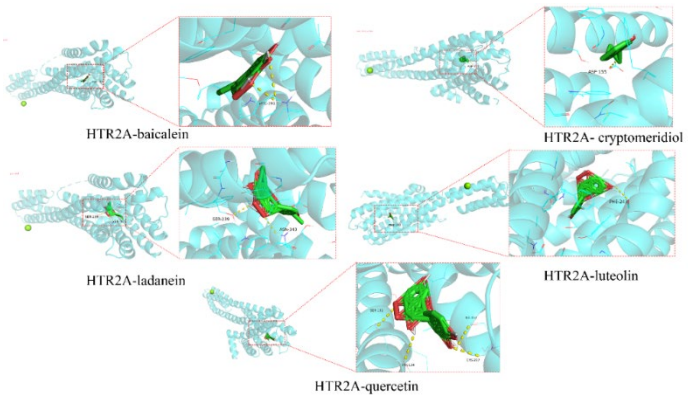

Figure 8: The docking results of HTR2A with key compounds.

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4. Discussion

Through extensive screening using TCMSP, HERB, ETCM databases, and related literature, we identified 67 active compounds in traditional Chinese medicines and 87 potential targets for treating insomnia. The top three Chinese medicinal components ranked by Degree value are apigenin, hispidulin, and kaempferol. These active ingredients, all belonging to the flavonoid compound category, have the capacity to directly or indirectly influence the balance of neurotransmitters such as 5-HT (serotonin), DA (dopamine), NE (norepinephrine), and GABA (gamma-aminobutyric acid). These neurotransmitters play crucial roles in regulating the sleep cycle, promoting sleep depth, and maintaining sleep quality[13-15].

Numerous studies have demonstrated that flavonoids can enhance sleep by boosting the activity of the GABAergic neurotransmitter system[16, 17]. Oxidative stress and inflammation are considered potential aggravating factors for insomnia and other sleep disorders[18]. Flavonoids improve sleep quality by modulating oxidative stress and inflammation. Apigenin, found in various fruits, vegetables, herbs, and plant-based beverages, is celebrated for its health-promoting effects, including potential benefits in treating chronic conditions such as diabetes, Alzheimer's disease, depression, and insomnia[19]. Thanks to its antioxidant, anti-inflammatory, and anticancer properties, apigenin's therapeutic potential spans a wide range of activities. In one study examining the effects of chamomile extract containing more than 2.5 mg of apigenin on sleep and daytime symptoms in patients with chronic insomnia, significant improvements were noted. High levels of quercetin and kaempferol are well-known for their anti-inflammatory, antioxidant, and potential neuroprotective actions. Their effects on the central nervous system, including potential antidepressant activity and modulation of GABA and NMDA receptors, are noteworthy. These receptors are involved in mood regulation and could indirectly affect sleep patterns[20].

Through PPI network analysis, the top three targets identified based on their Degree values were SLC6A4, SLC6A3, and DRD2. In the "drug-component-target" network, the three highest-ranked targets according to their Degree values were CYP1B1, ESR1, and ABCB1.

The SLC6A4 gene encodes the serotonin transporter (SERT), which plays a critical role in regulating serotonin levels in the brain[21]. It features a functional polymorphism known as the serotonin transporter-linked polymorphic region (5-HTTLPR), consisting of short (S) and long (L) alleles, each with 14 or 16 tandem repeats. A double-blind, placebo-controlled, crossover study assessed the effects of one week of placebo treatment (1000 mg daily) and one week of tryptophan supplementation (1000 mg daily) on both subjective (sleep diaries) and objective (activity monitoring) sleep in individuals homozygous for the 5-HTTLPR S allele (n=47) and L allele (n=51). The results supported the sleep-promoting effects of tryptophan, showing that it improved objective sleep efficiency and post-sleep wakefulness regardless of allele variation. After consuming tryptophan compared to the placebo, the 5-HTTLPR S allele group showed marginal improvements in subjective sleep quality, whereas the L allele group did not[22].

The ABCB1 gene encodes P-glycoprotein, a crucial drug transporter that influences the brain distribution and action of various drugs, including antidepressants[23]. Research indicates that ABCB1 affects the occupancy of the serotonin transporter by serotonin reuptake inhibitors in patients with depression, thereby impacting drug efficacy[24]. In a large clinical trial involving 683 patients who had received at least two weeks of antidepressant treatment, genotyping of 10 single nucleotide polymorphisms (SNPs) within the ABCB1 gene revealed that the functional SNP rs10245483 significantly affected the treatment outcomes with escitalopram, sertraline, or venlafaxine XR (all P-glycoprotein substrates). This study suggests a close relationship between genotype and the response to specific antidepressants, as well as side effects, without being affected by cognitive impairments[25].

5. Conclusion

In conclusion, the "Memie Anshen Formula" may play a beneficial role in treating insomnia, potentially through mechanisms involving the CYP1B1, ESR1, ABCB1, and HTR2A targets. Further experimental and clinical validation by the research team is awaited to fully ascertain these effects.

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