Potential Mechanisms of Shu Gan Jie Yu Capsule in the Treatment of Mild to Moderate Depression Based on Systemic Pharmacology and Current Evidence

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Background. Shu Gan Jie Yu (SGJY) capsule has a good effect on relieving depressive symptoms in China. However, the mechanism of action is still unclear. Therefore, systemic pharmacology and molecular docking approaches were used to clarify its corresponding antidepressant mechanisms. Methods. Traditional Chinese Medicine Database and Analysis Platform (TCMSP), the Encyclopedia of Traditional Chinese Medicine (ETCM), and Swiss Target Prediction servers were used to screen and predict the bioactive components of the SGJY capsule and their antidepressive targets. Mild to moderate depression (MMD) related genes were obtained from GeneCards and DisGeNET databases. A network of bioactive components-therapeutic targets of the SGJY capsule was established by STRING 11.5 and Cytoscape 3.9.0 software. Gene function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed by utilizing Database for Annotation, Visualization, and Integrated Discovery (DAVID) platform. Active components were taken to dock with the hypothetical proteins by iGEMDOCK and SwissDock, and the docking details were visually displayed by UCSF Chimera software. Then, the related research literature of the SGJY capsule was reviewed, summarized, sorted, and analyzed, including experimental evidence and clinical experience. Results. Seven active components and 45 intersection targets were included in the study. PPI network had genuinely uncovered the potential therapeutic targets, such as AKT1, HSP90AA1, ESR1, EGFR, and PTGS2. KEGG pathway analysis showed that the mechanism of the SGJY capsule on MMD was mainly involved in the PI3K-Akt signaling pathway. Conclusions. In this study, we have successfully predicted the biochemically active constituents, potential therapeutic targets, and comprehensively predicted the related drug-gene interaction of the SGJY capsule for treating MMD and provided a basis for subsequent experiments.

1. Introduction

Depression is one of the most disabling disorders worldwide with poor quality of life. It affects human social function, and imposes a heavy economic burden on individuals, families, communities, and countries. Due to the increasing social pressure and the role of various other factors, mild to moderate depression (MMD), as an early stage of depression, shows a trend of younger age [1]. Currently, selective serotonin reuptake inhibitors (SSRIs) have been widely used in clinical treatment, but their therapeutic effectiveness is only limited at ~65% [2]. Thus, more effective drugs with less adverse reactions are expected to be developed in the future. Nowadays, traditional natural herbs are usually used to relieve depression and balance emotions [3].
Systematic review and meta-analysis have provided effective evidence that Shu Gan Jie Yu (SGJY) capsule showed an effective intervention for essential hypertension patients with insomnia, anxiety or depression in recent years. And it is widely used in the treatment of MMD. The SGJY capsule mainly concludes two Chinese herbs, Acanthopanax senticosus (Rupr. & Maxim.) Harms (ASH) and Hypericum perforatum L. (HPL). The antidepressant mechanism of ASH may be mediated via the central monoaminergic neurotransmitter system and cAMP response element-binding (CREB) protein expression. Therefore, administration of ASH may be beneficial for patients with depressive disorders [4]. HPL, widely known as St. John’s wort, is commonly used in clinical practice for its antidepressant properties, as well as anxiolytic its properties[5]. In addition, HPL extract is effective in treating MMD and is safer than SSRIs [6]. Although the SGJY capsule has achieved good clinical efficacy in the treatment of MMD, its mechanism of action is still unclear.

With the rapid development of chemoinformatics and bioinformatics, systematic pharmacology, a technology based on computer simulation, has become a developing interdisciplinary. It applies network pharmacology to indicate the molecular mechanisms of Traditional Chinese Medicine (TCM), and has been widely used in screening bioactive components in TCM. In general, systemic pharmacology technology could evaluate the pharmacological effects and reveal the underlying relationship among active components, potential targets, and multiple diseases [7].

In this study, a systemic pharmacology-based strategy combined with molecular docking approach had been employed to predict bioactive components, potential gene targets, and related signal pathways of the SGJY capsule on depression treatment. The flowchart of research approach is shown in Figure 1.

2. Methods

2.1. Screening for Active Components of the SGJY Capsule. Traditional Chinese Medicine Database and Analysis Platform (TCMSP, https://www.tcmsp-e.com/) and the Encyclopedia of Traditional Chinese Medicine (ETCM, https://www.tcmip.cn/ETCM/index.php/Home/) were used to screen components of ASH and HPL [8]. The screening criteria were set as oral bioavailability (OB) greater than or equal to 30% and drug-likeness property (DL) greater than or equal to 0.18 [9]. The molecular structure was reconfirmed by PubChem platform (https://pubchem.ncbi.nlm.nih.gov/) and saved in .mol2 and SMILES format for further study.

2.2. Potential Targets Prediction. Active components were submitted to Swiss Target Prediction platform (https://www.swistargetprediction.ch/) based on SMILES format with parameter Probability ≥0.6 in prediction results in order to obtain high-quality targets [10]. “Homo sapiens” was used as selected species. After removing duplicate genes, potential targets related with active components of the SGJY capsule were obtained. MMD-related targets were collected individually from the DisGeNET (https://www.disgenet.org/home/) and GeneCards (https://www.genecards.org/) databases with the keywords “psychotic depression, mental depression, depressive disorder, mild depression, and moderate depression.” All the targets were standardized in the UniProt database (https://www.uniprot.org/).

2.3. Network Construction and Gene Analysis. SGJY-related and MMD-related targets were all imported into the Venny 2.1 system (https://bioinfogp.cnb.csic.es/tools/venny/). The intersection targets were selected as the potential targets for further analysis. A protein–protein interaction (PPI) network was constructed by using the STRING 11.5 platform (https://string-db.org/), “Organism” was set to “Homo sapiens.” An interaction with medium confidence (0.4) was collected. The network was visually displayed by the Cytoscape 3.9.0 software. Then GO function and KEGG enrichment analyses were performed with the DAVID platform (https://david.ncifcrf.gov/tools.jsp). The identifier and species were selected as “official gene_symbol” and “Homo sapiens,” respectively. The enrichment results, including molecular functional (MF), cell component (CC), biological process (BP), and KEGG pathway enrichment, were obtained and visualized by using imageGP platform (https://www.ehbio.com/ImageGP/index.php/Home/Index/index.html) as the bubble graph with p value <0.05 [11].

2.4. Molecular Docking. Crystal structures of core proteins were obtained from the RCSB Protein Data Bank (PDB, https://www.rcsb.org/) with high resolution and score. Water molecules were removed from the structure. Potential candidate components of the SGJY capsule in .mol2 format were taken as ligands. Molecular docking was mainly completed by iGEMDOCK 2.1 with default parameters. Afterward, the most potential protein with associated active ingredients at the low energy was used to dock on the SwissDock platform (https://www.swissdock.ch/docking/), and the results were visually displayed by the UCSF Chimera 1.15 software.

2.5. Literature Collection and Analysis. Literature search was performed via PubMed database (https://pubmed.ncbi.nlm.nih.gov/) with the term “Shu gan jie yu.” All relevant literature were collected, organized, categorized, and divided into experimental evidence and clinical practice.

3. Results

3.1. Collection and Screening Bioactive Components of the SGJY Capsule. Ten active components of the SGJY capsule were screened out via the TCMSP and ETCM database with the thresholds of OB ≥30% and DL ≥0.18 properties (Table 1), while ASH and HPL have a common compound named 3-epi-beta-sitosterol (PubChem CID 12303645). However, 3-epi-beta-sitosterol, ethyl oleate, and acanthiside B were excluded because of no gene interaction in the
network. Finally, 7 bioactive molecules were collected for further analysis, including betulinic acid, sesamin, kaempferol, cianidanol, luteolin, (+)-epicatechin, and quercetin.

3.2. Determination of Common Targets. After excluded duplicate data, 116 candidate targets of main components were collected, 7041 and 1747 MMD-related targets were identified from GeneCards and DisGeNET databases, respectively. 45 intersection targets were shown as a Venn diagram (Figure 2).

3.3. PPI Network Construction and Analysis. Forty-five intersection genes correlated with MMD were analyzed by the STRING database, and PPI network was established (Figure 3(a)). A total of 45 nodes and 70 edges were embodied with the average node degree 8.53 and p value <0.01. The most-connected targets were AKT1, HSP90AA1, ESR1, EGFR, PTGS2, GSK3B, MMP9, MMP2, IGF1R, KDR, APP, MCL1, PIK3R1, and MAPT with larger degree (degree >10), as shown in Table 2 and Figure 3(b). The network of herbs-components-targets was constructed, including 2 herbs, 7 components, and 45 potential targets, in which the blue hexagons correspond to the putative targets and bioactive components are in pink (Figure 4).

3.4. Gene Function and KEGG Pathway Enrichment Analyses. To further capture the relationships between the terms, the DAVID platform was used to perform gene function and KEGG pathway analyses with p value <0.05. The main biological processes contained signal transduction, negative regulation of apoptotic process, and protein autophosphorylation (Figure 5(a)). Cellular components

**Table 1:** Basic information of the main active components of the SGJY capsule.

| Herbs | PubChem CID | Chemical name       | OB (%) | DL  |
|-------|-------------|---------------------|--------|-----|
| ASH   | 12303645    | 3-Epi-beta-sitosterol| 36.91  | 0.75|
|       | 5363269     | Ethyl oleate        | 32.40  | 0.19|
|       | 64971       | Betulinic acid      | 55.38  | 0.78|
|       | 72307       | Sesamin             | 56.55  | 0.83|
|       | 443024      | Acanthoside B       | 43.35  | 0.77|
| HPL   | 12303645    | 3-Epi-beta-sitosterol| 36.91  | 0.75|
|       | 5280863     | Kaempferol          | 41.88  | 0.24|
|       | 9064        | Cianidanol          | 54.83  | 0.24|
|       | 5280445     | Luteolin            | 36.16  | 0.25|
|       | 182232      | (+)-Epicatechin      | 48.96  | 0.24|
|       | 5280343     | Quercetin           | 46.43  | 0.28|

**Figure 1:** The research flowchart of antidepressant mechanism of the SGJY capsule.
Figure 2: Diagram of overlapping target genes between the SG/Y capsule and MMD.

Figure 3: Continued.
mainly involved plasma membrane, cytoplasm, and nucleus (Figure 5(b)). Protein, ATP, and identical protein binding were the main molecular functions of intersection genes (Figure 5(c)). The mechanisms of the SGJY capsule in the treatment of MMD included PI3K-Akt, Ras, and estrogen signaling pathways (Figure 5(d)). Among them, the PI3K-Akt pathway was the most potential signaling pathway.

3.5. Molecular Docking. PPI network construction and gene analysis indicated that the potential targets of the SGJY capsule against MMD were based on their degree. They were selected to dock with 7 active components (betulinic, cianidanol, (+)-epicatechin, kaempferol, luteolin, quercetin, and sesamin). Fluoxetine, which was a SSRI and widely used in clinical practice, was used as a positive control [12]. The lowest binding energy shows the most stable combination. The value of fitness was used to evaluate the binding level. The total energy was regarded as a predicted pose in the binding site, which included Van Der Waal (VDW), hydrogen bonding (H-bond) and electrostatic energy, so 

\[ E_{\text{total}} = E_{\text{VDW}} + E_{\text{H-bond}} + E_{\text{electrostatic}} \]

It was interesting to note that most compounds had a better bonding ability to potential targets than fluoxetine, as shown in Figure 6. Moreover, (+)-epicatechin, kaempferol, luteolin, quercetin, and sesamin were all closely bound to protein MMP9, and
Table 2: Potential targets of the SGJY capsule against MMD (degree > 10).

| No. | UniProt ID | Gene names | Protein names | PDB ID | Degree |
|-----|------------|------------|---------------|--------|--------|
| 1   | P31749     | AKT1       | RAC-alpha serine/threonine-protein kinase | 7NH5   | 28     |
| 2   | P07900     | HSP90AA1   | Heat shock protein HSP 90-alpha | 3Q0I   | 24     |
| 3   | P03372     | ESR1       | Estrogen receptor | 5FQV   | 23     |
| 4   | P00533     | EGFR       | Epidermal growth factor receptor | 5GNK   | 22     |
| 5   | P35354     | PTGS2      | Prostaglandin G/H synthase 2 | 5F19   | 20     |
| 6   | P49841     | GSK3B      | Glycogen synthase kinase-3 beta | 6YS5   | 18     |
| 7   | P14780     | MMP9       | Matrix metalloproteinase-9 | 6EM5   | 17     |
| 8   | P08253     | MMP2       | 72 kDa type IV collagenase | 3AYU   | 15     |
| 9   | P08069     | IGF1R      | Insulin-like growth factor 1 receptor | 1P4O   | 15     |
| 10  | P35968     | KDR        | Vascular endothelial growth factor receptor 2 | 6GQQ   | 13     |
| 11  | P05067     | APP        | Amyloid-beta precursor protein | 4PWQ   | 13     |
| 12  | Q07820     | MCL1       | Induced myeloid leukemia cell differentiation protein Mcl-1 | 6OQD   | 13     |
| 13  | P27986     | PIK3R1     | Phosphatidylinositol 3-kinase regulatory subunit alpha | 2IUG   | 13     |
| 14  | P10636     | MAPT       | Microtubule-associated protein tau | 6ODG   | 11     |

Figure 4: The network of herbs-components-targets. The red shows the Chinese herbs of the SGJY capsule, the cyan displays the active components of the SGJY capsule, and the blue shows the most potential targets of the SGJY capsule in the treatment of MMD. Furthermore, the density of lines represents the interaction relationship between different protein targets.
sesamin had the better bonding mode with the MMP9 protein than fluoxetine based on binding energy (Figure 7).

### 3.6. Literature Collection and Analysis

#### 3.6.1. Experimental Evidence of the SGJY Capsule

Shu Gan Jie Yu capsule mainly contains two Chinese herbs, *Acanthopanax senticosus* (Rupr. & Maxim.) Harms (ASH) and *Hypericum perforatum* L. (HPL). Many evidences show that ASH and HPL play an important role in the treatment of MMD.

Jin et al. found that ASH extract significantly elevated the levels of 5-hydroxytryptamine, norepinephrine, and dopamine in the whole brain of mice and up-regulated the level of CREB protein. It might exert antidepressant effects via the central monoaminergic neurotransmitter system and CREB protein expression [13]. *In vitro* studies had shown that ASH

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| Ligand       | Protein | AKT1  | APP   | ESR1  | HSP90AA1 | IGF1R | KDR   | MAPT  | MCL1  | MMP2  | MMP9  | PIK3R1 | PTGS2 |
|--------------|---------|-------|-------|-------|----------|-------|-------|-------|-------|-------|-------|--------|-------|
| Betulinic    | -112.17 | -86.64| -78.39| -89.04| -89.16   | -88.83| -91.37| -93.91| -97.72| -78.86| -103.10|        |       |
| Cianidanol   | -100.48 | -89.77| -93.86| -91.43| -92.18   | -93.90| -89.64| -100.53| -106.52| -108.97| -85.14| -100.51|       |
| (+)-Epicatechin| -104.78 | -86.03| -101.08| -115.92| -93.09   | -98.01| -84.68| -98.89| -107.14| -133.48| -86.47| -119.26|       |
| Kaempferol   | -108.43 | -88.42| -93.84| -112.88| -88.64   | -89.75| -79.09| -92.43| -92.80| -123.30| -81.93| -110.48|       |
| Luteolin     | -103.98 | -82.95| -94.78| -108.92| -82.94   | -94.31| -83.16| -104.34| -94.12| -124.98| -81.65| -101.88|       |
| Quercetin    | -107.49 | -91.78| -97.87| -104.89| -94.15   | -95.53| -82.86| -103.88| -99.85| -124.94| -88.70| -104.85|       |
| Sesamin      | -111.68 | -96.93| -100.91| -123.21| -106.46  | -99.58| -93.93| -109.62| -107.40| -144.74| -87.16| -117.69|       |
| Fluoxetine   | -96.14  | -80.01| -77.85| -68.43| -68.95   | -68.31| -83.96| -89.19| -74.51| -81.78| -59.66| -104.15|       |

Figure 5: GO enrichment and KEGG pathway analyses. (a) Biological process (BP) terms, (b) cellular component (CC) terms, and (c) molecular function (MF) terms of GO enrichment analysis (top 10). (d) KEGG pathway enrichment (top 10). The color of the dot is displayed in a gradient from red to green according to the ascending order of the number of gene counts. The longitudinal axis represents the percentage of the number of enriched genes to the total number of genes. p value <0.05.

Figure 6: Molecular docking results. Red color represents low docking score, and blue represents high docking score. The lowest value indicates the most stable conformation (kcal/mol).
extract significantly increased the cell viability, suppressed the apoptosis of PC12 cells, and up-regulated CREB protein expression. Neuroprotective effect might be one of the acting mechanisms that accounts for the in vivo antidepressant activity of ASH [14]. The induction of HO-1 expression protected cells against glutamate-induced neuronal cell death. ASH extract could regulate HO-1 expression through the p38-CREB pathway and translocation of Nrf2, and played an important role in the generation of anti-neuroinflammatory and neuroprotective responses [4]. Moreover, it had beneficial effects on depression behaviors and restored both altered c-fos expression and hypothalamic-pituitary-adrenal (HPA) activity which associated with stress, and may be a novel agent for the treatment of stress-related disorders [15].

HPL, popularly called St. John’s wort, is used as a medicinal plant for MMD, and is more effective than placebo or some antidepressant drugs. Di Pierro, et al. found that multifractionated hypericum extract has better clinical outcomes in subjects with depression without determining an increased risk of toxicity or reduced tolerability [16]. HPL could regulate the genes that control HPA axis function and influence, like conventional antidepressants. Thus, at least in part, it plays stress-induced effects on neuroplasticity and neurogenesis [17]. For patients with mild to moderate depression, St John’s wort has comparable efficacy and safety when compared to SSRIs [18]. Most of HPL extracts have been shown to be significantly more effective than placebo with at least similar efficacy and better tolerability compared to standard antidepressant drugs. It is a safe and effective way to treat MMD over long periods of time with less adverse effects, and seems especially suitable for a relapse prevention [19–21].

3.6.2. Clinical Practice of the SGJY Capsule. The SGJY capsule is widely used in clinical practice and has achieved very good clinical results in MMD. Clinical efficacy and safety of the SGJY capsule in patients with acute myocardial infarction and depression. Significantly lower adverse event rate was observed in the Shu Gan Jie Yu group. The SGJY capsule has a reliable effect and high safety in patients with depression [22]. In addition, it is very effective for treatment of senile depression [23].

The SGJY capsule is also an effective intervention for essential hypertension patients with insomnia, anxiety, and depression [3]. Yao et al. found that the SGJY capsule significantly reduced the depressive symptoms and improved cognitive functions in poststroke depressive patients through alteration of brain dynamics [24].

4. Discussion

Seven bioactive components of the SGJY capsule, including betulinic, cianidanol, (+)-epicatechin, kaempferol, luteolin, quercetin, and sesamin, had been successfully obtained by systemic pharmacology strategy. Recent studies also confirmed the antidepressant effects of these compounds.

Figure 7: The best binding modes of sesamin (a) and fluoxetine (b) with MMP9 protein by SwissDock. Visualization is performed using UCSF Chimera.
Kaempferol and quercetin had been reported to relieve symptoms of depression and exhibited antidepressive effects through acting on interleukin-6 (IL6), mitogen-activated protein kinase 1 (MAPK1), signal transducer, and activator of transcription 3 (STAT3) and transcription factor AP-1 (JUN) [25]. Betulinic produced a significant antidepressant-like effect [26]. Cianidanol, also called (+)-catechin, together with kaempferol and quercetin showed potential capacity in depression management [27]. Luteolin could prevent both neuroimmune responses and behavioral abnormalities including major depressive disorder, which was induced by visceral inflammation [28]. Sesamin inhibited chronic unpredictable mild stress (CUMS)-induced mice depressed-like behaviors and anxiety, which retained immobility and prevented stress-induced decrease of 5-HT and NE in the striatum and serum. Moreover, sesamin treatment significantly prevented CUMS-induced neuroinflammation by inhibiting over-activation of microglia and expressions of inflammatory mediators including iNOS, COX-2, TNF-α, and IL-1β in stressed mice hippocampus and cortex [29]. Therefore, multiple active components of the SGJY capsule may exert therapeutic effects on MMD.

PPI network analysis showed that 14 core targets correlated bioactive components had been determined, such as AKT1, HSP90AA1, ESR1, EGFR, PTGS2, GSK3B, MMP9, MMP2, IGF1R, KDR, APP, MCL1, PIK3R1, and MAPT. Some studies had reported that the AKT1 gene was strongly associated with antidepressant treatment [30, 31], which further confirmed our results. And PTGS2 [32, 33], EGFR [34], ESR1 [35, 36], APP [37], IGF1R [38, 39], KDR [40], GSK3B [41, 42], MAPT [43], and PIK3R1 [44] played very important roles in prevalence and progression of depression. It was verified that HSP90AA1 was up-regulated in patients with depression, which correlated with elevated levels of VEGF, VEGFR2, PI3K, and AKT1 [45]. Some studies showed that MMP-2 and MMP-9 genes had relative lower expression on both mRNA and protein levels in depression [46, 47]. MMP9, a key protein for extracellular matrix degradation, was significantly correlated with depressive symptoms [38, 39]. Our study found that most of the bioactive components of the SGJY capsule had good binding capacity to MMP9, which indicated that MMP9 played a very important role on SGJY-treated MMD.

Signal transduction has been reported to be closely involved in antidepressant treatment. Gene function and KEGG results indicated that the main molecular mechanism of the SGJY capsule in the treatment of MMD was the PI3K-Akt signaling pathway, KDR, CDK6, IGF1R, EGFR, INSR, GSK3B, HSP90AA1, PIK3CG, MCL1, PIK3R1, and AKT1 genes were enriched in it. Quercetin, luteolin, and kaempferol had been confirmed to be effective in the treatment of MMD by in vivo experiments. The potential PI3K-Akt signaling pathway, a classic signaling pathway in cells, closely relates to the biological process of depression [43, 48]. It regulates fundamental cellular functions such as transcription, translation, proliferation, growth, and survival. In addition, the SGJY capsule might exert therapeutic effects on MMD via Ras, estrogen, and Rap signaling pathways. Homologous Ras-family small GTPases, including Ras, Rap2, and Rap1, played a different role and presented signal diversity and specificity. Ras signals long-term potentiation via endoplasmic reticulum PI3K and lipid raft ERK, whereas Rap2 and Rap1 signal dephosphatination and long-term depression via bulk membrane JNK and lysosome p38MAPK, respectively [49]. Thus, Ras-family small GTPases related signaling pathways, including Ras-Raf-MAPK [50], Ras-ERK-MAPK [51], and Rap1-MKK3/6-p38 MAPK [52], may be involved in explaining the disease etiology, the clinical symptom, and treatment response of stress-induced depression [53]. Increasing evidence had been manifested that the disturbances of estrogen signaling pathway occurred in psychiatric disorders, especially in female depression [54]. Hence, the role of multiple signaling pathways is under consideration. Further study is warranted to reveal the relationship between core targets activated by potential bioactive components of the SGJY capsule and different related signaling pathways.

Due to the limitations of compounds screening and accuracy of target prediction, the results obtained in this study are general [55]. Although there is some evidence, many in vivo and in vitro experiments are still needed for verification. In short, our study portrayed the groundview of the SGJY capsule in the treatment of mild to moderate depression.

5. Conclusion

In this study, seven bioactive components of the SGJY capsule have been identified by a systemic pharmacology-based strategy and the intersection targets corresponding to these components and their therapeutic mechanism of MMD have been revealed in detail by the PPI network and pathway enrichment analyses. The result of molecular docking showed that sesamin had a better bonding mode with the MMP9 protein than fluoxetine. In general, bioactive components and the main therapeutic mechanism of the SGJY capsule in the treatment of MMD were successfully predicted, which might provide valuable guidance for further pharmacological research of the SGJY capsule on MMD.

**Abbreviations**

ASH: Acanthopanax senticosus (Ruapr. & Maxim.) Harms
BP: Biological process
CC: Cell component
CREB: CAMP response element-binding
CUMS: Chronic unpredictable mild stress
DAVID: Database for annotation, visualization, and integrated discovery
DL: Drug-likeness
ETCM: Encyclopedia of Traditional Chinese Medicine
GO: Gene Ontology
HB: Hydrogen bond
HPA: Hypothalamic-pituitary-adrenal
HPL: Hypericum perforatum L.
HT: 5-hydroxytryptamine
KEGG: Kyoto encyclopedia of genes and genomes
MF: Molecular function
MMD: Mild to moderate depression
MMP-2: Matrix metalloproteinase 2
MMP-9: Matrix metalloproteinase-9
NE: Norepinephrine
OB: Oral bioavailability
PDB: Protein data bank
PI3K-Akt: Phosphatidylinositol 3-kinase-protein kinase B
PPI: Protein-protein interaction
ROS: Reactive oxygen species
SDF: Structure-data file
SGJY: Shu Gan Jie Yu capsule
capsule:
SSRIs: Selective serotonin reuptake inhibitors
TCM: Traditional Chinese medicine
TCMSP: Traditional Chinese medicine database and analysis platform.

Data Availability
The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure
Taiping Li and Tian Qiu are the co-first authors.

Conflicts of Interest
The authors declare that there are no conflicts of interest.

Authors’ Contributions
Hong Xiao and Ning Yang carried out conceptualization, review, editing, resources, supervision, and project administration. Tian Qiu and Yanyan Zeng were responsible for methodology, investigation, formal analysis, and data curation. Bing Kang was involved in methodology, formal analysis, and data curation. Taiping Li and Xianglong Tang performed conceptualization, review, editing, methodology, investigation, and writing of the original draft. Tian Qiu and Taiping Li contributed equally to this work.

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