Novel Combination of HuanglianJiedu Decoction in Behavioral and Psychological Symptoms of Dementia in Alzheimer's Disease

Su-Ya Ma  
Beijing University of Chinese Medicine

Xu Wang  
Beijing University of Chinese Medicine

Jing Shi  
Department of Neurology, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, 100007, China

Research Article

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Abstract

Alzheimer's disease (AD) is characterized by progressive cognitive decline. Besides cognitive deficit, AD is also characterized by behavioral and psychological symptoms in dementia (BPSD). However, therapeutic management of BPSD remains challenging. HuanglianJiedu decoction (HLJDD), a traditional Chinese prescription, consisting of four herbs, is applied to treat AD, especially AD with BPSD. Though HLJDD, has the traditional combination with the principal herb *Coptidis rhizoma* (Huang-lian), it might, however, not be suitable for treating BPSD. Elucidating the mechanism underlying each herb is critical to the disease-matched combination of HLJDD. In this study, network pharmacology was used to determine the targets and biological processes regulated by HLJDD in the treatment of BPSD. Moreover, molecular docking was utilized to evaluate the binding activity between the herbs' main active ingredients and neurotransmitter receptors. The results showed that *Scutellariae radix* (Huang-qin) and *Phellodendri chinensis cortex* (Huang-bai) exhibited better anti-BPSD effects when compared to *Coptidis rhizoma* and *Gardeniae fructus* (Zhi-zi). *Scutellariae radix* exhibited superior anti-neuroinflammation functions, while *Phellodendri chinensis cortex* showed a higher binding affinity to the dopamine D2 receptor (DRD2) and 5-hydroxytryptamine receptor 2A (HTR2A). *Coptidis rhizoma* and *Gardeniae fructus* were better in neuronal signaling. In conclusion, for treating BPSD, *Scutellariae radix* and *Phellodendri chinensis cortex* are the principal herbs while *Coptidis rhizoma* and *Gardeniae fructus* are the ancillary herbs.

1. Introduction

In traditional Chinese medicine (TCM), the combination of herbs into a prescription to enhance their overall therapeutic effects or eliminate the adverse effects[1], is referred to as TCM combination. Although prescriptions have conventional combinations, it is essential to consider novel combinations for different diseases. In this study, we propose an innovative method that is based on molecular mechanism for determining herbs combination. We investigated the novel combination of HLJDD in BPSD.

The prevalence of BPSD, including anxiety, agitation, aggression, irritation, depression, apathy, disinhibition, delusions, or hallucinations in AD patients is more than 90%[2]. Molecules involved in the pathogenesis of BPSD have been widely studied. Neuroinflammation, a response that involves neurons and microglia, has been reported to characterize several neurodegenerative diseases and neuropsychiatric conditions, resulting in the elevated production of pro-inflammatory cytokines, like IL-6, TNF-α, IL-8, and IL-4. Notably, microglia activation is the first sign of neuroinflammation. Activated microglia can release various oxidants such as reactive oxygen species and activate several genes and proteins, such as inducible nitric oxide synthase[3]. Neurotransmitters and their receptors are also considered to play a crucial role in BPSD[4]. Evaluation of genetic risk factors provide a powerful approach for elucidating the mechanisms underlying BPSD. APOE epsilon4, the most common genetic risk factor for the late-onset of AD, elevates the risk of BPSD[5]. However, the efficacy of antipsychotics for the treatment of BPSD is scanty. Antipsychotic drugs used in the clinical management of BPSD have extrapyramidal severe side effects (EPS). Memantine, an NMDA receptor antagonist for treating moderate-to-severe AD, inhibits antipsychotic-induced EPS[6], but is controversial for treating BPSD. The current primary therapeutic options for AD, acetylcholinesterase inhibitors, are not effective for treating BPSD[7]. Several researchers turn their attention to natural products as an alternative or complementary method to BPSD for their clinical efficacy with minimal side effects.

BPSD has different TCM syndrome differentiation. “Toxin damaging brain collateral” an essential BPSD differentiation, was proposed by Yongyan Wang. For this syndrome differentiation, brain collateral is injured by re toxins. For the treatment, purging re for removing toxins is commonly used. HLJDD, which is composed of *Scutellariae radix*, *Coptidis rhizoma*, *Phellodendri chinensis cortex*, and *Gardeniae Fructus*, is a classic prescription for heat-clearance and detoxification. Studies have documented that HLJDD is frequently used in AD management[8], especially with BPSD[9]. While the TCM physicians seldom treat BPSD with whole herbs in HLJDD or with HLJDD only. They prefer to choose two or more principal herbs in HLJDD with other syndrome-match herbs. According to HLJDD’s traditional combination, the TCM physicians now prefer to choose *Coptidis rhizoma* as the primary herb to treat BPSD. However, in this research, *Scutellariae radix* and *Phellodendri chinensis cortex* are the remedying herbs in BPSD. So we put forward that the traditional combination of prescription need refers to the novel combination with modern technology. To elucidate HLJDD’s combination in treating BPSD, we used network pharmacology and molecular docking to provide useful drugs for BPSD therapeutics by emphasizing their molecular activities (Figure 1).

2. Material And Methods

2.1. Determination of active ingredients and their matched potential target proteins. A natural plant contains various chemical compounds. We used the TCM systems pharmacology database and analysis platform (TCMSP: https://tcmspw.com/index.php) to determine the main active ingredients in the herbs. Compounds were filtered by oral bioavailability (OB) ≥ 30%, drug-likeness (DL) ≥ 0.18, and drug half-life (HL) ≥ 4 h. The potential molecular targets for the active compounds were predicted using the search tool for interactions of chemicals database (STITCH, http://stitch.embl.de/), with the species limited to “Homo sapiens.”

2.2. Potential targets prediction for BPSD. BPSP-associated protein targets were identified using the GeneCards database (http://www.genecards.org/) [10]. These target proteins exhibited a higher rank score, and a higher correlation with BPSD. The keywords used in the search were “behavioral and psychological symptoms of dementia in Alzheimer’s disease.” The top 50% of the predicted targets were selected as potential BPSD targets.

2.3. Network construction and analysis. We constructed the "compounds-targets-BPSD" networks by Cytoscape 3.7.2 software [11]. The .csv format files whose data combined target compounds and BPSD targets were imported into Cytoscape. The node size was based on the target proteins score values.
as provided by the GeneCards database. Overlapping targets between active compounds and BPSD were the herbs’ putative targets, and set with a red rectangle node. Memantine was used to identify the potential neurotransmitter receptors.

### 2.4. Enrichment analysis of target proteins

We performed Gene Ontology (GO) functional enrichment analysis using the ClueGO plugin [12], with the species limited to “Homo sapiens” and p < 0.05.

### 2.5. Molecular docking for active compounds with DRD2 and HTR2A

Memantine was selected as the active control medicine. The molecular mechanism of memantine on BPSD was determined by network pharmacology, same as the HLJDD herbs. The results showed that DRD2 and HTR2A were the targets of neurotransmitter receptors. Then molecular docking studies were conducted using AutoDock software [13] to evaluate the affinity of the active compounds bind with DRD2 and HTR2A neurotransmitter receptors. Crystal structures of the proteins were downloaded from the RCSB Protein Data Bank (http://www.rcsb.org/). PDB ID “6CM4” and “6A93”, whose ligand is Risperdal, were selected as DRD2 and HTR2A's crystal structure. Memantine, Risperdal, and HLJDD’s active compounds were then docked with DRD2 and HTR2A.

### 3. Results

#### 3.1. HLJDD’s main active compounds and potential target proteins

After searching the TCMSP database, we identified 80 compounds in HLJDD. Scutellariae radix, Coptidis rhizoma, Phellodendri chinensis cortex, and Gardeniae fructus have 32, 10, 27, and 11 ingredients, respectively. Then, these compounds were imported into the STITCH database to achieve the potential target proteins (Table 1).

#### Table 1: HLJDD’s active compounds and potential molecular target proteins

| Herbs                          | Active ingredients | Potential target proteins                                                                 |
|-------------------------------|--------------------|------------------------------------------------------------------------------------------|
| Scutellariae radix            | acacetin           | IL13/CYP1A2/VEGFA/UN:STAT1/NR1H2/SELE/CYP1A1/SLC35A1                                  |
| Scutellariae radix            | wogonin            | MMP9/MYCHMB1/MCL1/PTGS2/CDK9/GATA1/UCN1/PLSCR1/CLL                                    |
| Scutellariae radix            | baicalin           | MAPK1/ALOX15/CDK4/MMP2/PLAU/CYP1A2/AKT1/CYP3A4/ALOX12/MMP9                             |
| Scutellariae radix            | oroxylin a         | MAPK3/BDNF/HK2/SIRT3/CASP8/PP1/SLD2/PPAR1/NOS1                                          |
| Scutellariae radix            | Panicolin/skullcapflavone | CASP3                                    |
| Scutellariae radix            | beta-sitosterol    | DHR24/CASP3/ABCG5/SREBF2/ICAM1/ABCG8/CYP7A1/SREBF1/APOE/ABCB11                      |
| Scutellariae radix            | Stigmastanol       | TNF/LILB/ABCA1/ABCG8/NR1H2/SREBF2/ABCG5/NR1H3/SLC1B1                                |
| Scutellariae radix            | copisine           | PAWR/EXPO1/TNF/SLC35A1/ESF1                                                           |
| Coptidis Rhizoma              | quercetin          | MCL1/ATP5B/CYP1A1/HBCH/ECK/STK17/SLC2A1/CYP1B1/CYP2C8/PIM1                           |
| Coptidis Rhizoma              | berberine          | CCND1/CASP3/DPP4/TP53/AKT1/MAPK1/HMOX1/LDLR/PCSK9/ATP5G2                           |
| Coptidis Rhizoma              | copisine           | PAWR/TNF/SLC35A1/ESF1/XP01                                                           |
| Phellodendri chinensis cortex | berberine          | PCS9/ATP5G2/HMOX1/MAPK1/TP53/CASP3/AKT1/DPP4/LDLR/CCND1                           |
| Phellodendri chinensis cortex | copisine           | PAWR/EXPO1/TNF/SLC35A1/ESF1                                                           |
| Phellodendri chinensis cortex | rutecarpine        | CYP1A1/TNF/CYP1A2                                                               |
| Phellodendri chinensis cortex | Chelerythrine      | GADPH/PRKCE/PLA2G1/B2/CFTR/CH3L2/SELP/PLA2G2A/CORT/ABCB1                            |
| Phellodendri chinensis cortex | Stigmastanol       | IL10/TNF/SREBF2/ABCG8/SLC1B1/ABCG8/ABCG5/NR1H2/NR1H3/ABCA1                         |
| Phellodendri chinensis cortex | beta-sitosterol    | ABCG5/SREBF2/DHR24/CYP7A1/ABCB11/SLC35A1/ICAM1/SREBF1/ABCG8/APOE                  |
| Phellodendri chinensis cortex | Pumarine (protope) | HRH1/RF2/XIAO101                                                                     |
| Phellodendri chinensis cortex | quercetin          | CYP1B1/STK17/B/PIM1/SLC2A2/CYP1A1/HK2/ATP5B/HBCH/CYP2C8/MCL1                      |
| Phellodendri chinensis cortex | poriferast-5-en-3beta-ol/beta-sitosterol | CASP9/NR1H2/PPAR1/CASP3/ABCG8/ABCG5/ICAM1                                          |
| Phellodendri chinensis cortex | campesterol        | HSD3B2/ABCG8/ABCG5/CYP7A1/DHR24/CSN1/NR1H2                                          |
| Gardeniae fructus             | Sudan III          | CELA1/CELAR                                                                         |
| Gardeniae fructus             | quercetin          | CYP1B1/SLC2A2/STK17/CYP1A1/MCL1/PIM1/HBCH/ATP5B/ATP5FB                              |
| Gardeniae fructus             | beta-sitosterol    | SREBF1/CYP7A1/ABCB1/CASP3/ABCG5/APOE/ABCG8/SREBF2/DHR24/ICAM1                     |
| Gardeniae fructus             | kaempferol         | UGT1A9/UGT1A8/UGT3A1/UGT1A7/CYP1B1/CDK1/AHR/UGT1A3/NR1H2/RP56K3                    |
| Gardeniae fructus             | Stigmastanol       | ABCG8/SLN/TNF/NR1H2/NR1H3/SLC1B1/ABCG5/SLC1B1/ABCG5/ABCA1/SLC1B1                   |

#### 3.2. “Compounds-targets-BPSD” network and GO biological process analysis

In this network, the red rectangular nodes represent the key protein targets of the herbs. The targets for Scutellariae radix were the highest (24), followed by Phellodendri chinensis cortex (15). We used the GO biological process analysis to further study the herbs’ key protein targets. Figure 2 b and Table 2 show the biological processes of the key target proteins of Scutellariae radix, including positive regulation of smooth muscle cell proliferation, lipopolysaccharide-mediated signaling pathway, and regulation of neuroinflammatory responses, etc. Figure 3 b, c, d, and Table 3 show the biological processes of the key target proteins of Coptidis rhizoma. Its biological processes include regulation of cellular responses to cadmium ions, responses to nicotine, and negative regulation of macroautophagy. Figure 4 b, c, d, and Table 4 show the biological processes of the key target proteins for Phellodendri chinensis cortex. These processes include regulating responses to nicotine, glial cell apoptotic process, plasma lipoprotein particle, etc. Figure 5 b, c, d, and Table 5 show the biological processes of the key target proteins of Gardeniae fructus, which are mainly associated with the regulation of amyloid-beta formation, regulation of membrane protein ectodomain proteolysis and regulation of nitric oxide biosynthetic process.

#### Table 2: Biological functions of Scutellariae radix in BPSD
| Function                                      | Groups   | Group Genes                                                                 |
|-----------------------------------------------|----------|------------------------------------------------------------------------------|
| positive regulation of smooth muscle cell proliferation | Group 15 | AKT1|APOE|BDNF|CASP3|CCL2|HMGB1|ICAM1|IL10|IL13|IL6|JUN|MAPK1|MAPK3|MMP9|MYC|PTGS2|SOD2|STAT1|TNF|TNFSF11|VEGFA |
| lipopolysaccharide-mediated signaling pathway | Group 14 | AKT1|CCL2|ICAM1|IL10|IL13|IL6|JUN|MAPK1|MAPK3|MMP9|MYC|PTGS2|SOD2|TNF|TNFSF11 |
| regulation of neuroinflammatory response      | Group 13 | AKT1|CASP3|HMGB1|IL10|IL6|MAPK1|MAPK3|MMP9|PTGS2|SOD2|TNF|VEGFA |
| regulation of nitric oxide biosynthetic process | Group 12 | AKT1|HMGB1|ICAM1|IL10|IL13|IL6|JUN|MAPK3|PTGS2|SOD2|TNF|VEGFA |
| positive regulation of endothelial cell proliferation | Group 11 | AKT1|CASP3|HMGB1|ICAM1|IL10|IL6|JUN|MAPK3|PTGS2|SOD2|TNF|VEGFA |
| regulation of smooth muscle cell proliferation | Group 10 | AKT1|IL10|IL13|IL6|JUN|MMP9|MYC|PTGS2|SOD2|STAT1|TNF |
| regulation of nucleotide biosynthetic process  | Group 09 | MYC|NOS1|PTGS2 |
| positive chemotaxis                            | Group 08 | AKT1|CASP3|HMGB1|IL6|PTGS2|TNF|VEGFA |
| negative regulation of epithelial cell differentiation | Group 07 | ICAM1|IL13|MMP9|MYC|STAT1|VEGFA |
| regulation of endothelial cell proliferation    | Group 06 | AKT1|APOE|CCL2|HMGB1|IL10|JUN|PTGS2|STAT1|TNF|VEGFA |
| negative regulation of cysteine-type endopeptidase activity involved in apoptotic process | Group 05 | AKT1|HMGB1|IL6|MMP9|PTGS2|TNF|VEGFA |
| positive regulation of blood vessel endothelial cell migration | Group 04 | AKT1|CASP3|HMGB1|IL6|PTGS2|VEGFA |
| cellular response to interleukin-6              | Group 03 | ICAM1|IL6|STAT1 |
| vasodilation                                   | Group 02 | APOE|NOS1|SOD2 |
| regulation of DNA-templated transcription, initiation | Group 01 | CCL2|HMGB1|JUN |
| regulation of interferon-alpha production       | Group 00 | HMGB1|IL10|STAT1 |

**TABLE 3:** Biological functions of *Coptidis rhizoma* on BPSD

| Function                                      | Groups   | Group Genes                                                                 |
|-----------------------------------------------|----------|------------------------------------------------------------------------------|
| cellular response to cadmium ion              | Group 2  | AKT1|HMOX1|MAPK1 |
| response to nicotine                          | Group 1  | CASP3|HMOX1|MAPK1 |
| negative regulation of macroautophagy         | Group 0  | AKT1|HMOX1|TP53 |

**TABLE 4:** Biological functions of *Phellodendri chinensis cortex* in BPSD
### TABLE 5: Biological functions of *Gardeniae fructus* on BPSD

| Function                                      | Groups | Group Genes                     |
|-----------------------------------------------|--------|---------------------------------|
| regulation of amyloid-beta formation          | Group2 | APOE|CASP3|TNF                 |
| regulation of membrane protein ectodomain proteolysis | Group1 | APOE|IL10|TNF                 |
| regulation of nitric oxide biosynthetic process | Group0 | ICAM1|IL10|TNF                 |

3.3. "Compounds-targets-BPSD" network of memantine. Patients with moderate to severe AD exhibit relatively severe cognitive and psychological symptoms. N-Methyl-D-aspartic acid (NMDA) is one of the main therapeutic options. Memantine is the most common therapeutic choice for NMDA[14]. In our study, memantine was used as the reference drug. We established the "compounds-targets-BPSD" network of memantine to determine its potential mechanism in BPSD, especially for the neurotransmitter receptor. It was found that DRD2 and HTR2A were the neurotransmitter receptors associated with BPSD.

3.4. Results of molecular docking. Serotonin and its receptors, particularly the HTR2A, play roles in cognitive behaviors and psychiatric conditions such as depression, schizophrenia, and AD[4]. A multitarget-directed ligand, acting on HTR2A and DRD2, has been shown to exert an anti-aggressive and antipsychotic activity and is, therefore, a promising therapeutic option for BPSD [15]. In our study, herbs active ingredients were docked with DRD2 and HTR2A. The 3D structures of the active ingredients were downloaded from the TCMSP database in .mol2 format. They were later converted to .pdb format using the Open Babel GUI software[16]. The local search parameters and rigid filenames of the macromolecule models were used when docking. The software’s default values were set as our docking parameters. Grid box sizes were: DRD2: x-dimension: 62, y-dimension: 84, z-dimension: 126, spacing: 0.375, X center: 17.469, y center: 7.307, z center: 2.7. HTR2A: x-dimension: 126, y-dimension: 62, z-dimension: 84, spacing: 0.497, X center: 30.895, y center: 0.518, z center: 63.697. These parameters were minimally adjusted during docking.

We found that beta-sitosterol exhibited the lowest docking energy with DRD2 (-9.58 Kcal/mol) and HTR2A (-8.2 Kcal/mol) when compared to the other compounds, including memantine and Risperdal. Stigmasterol, chelerythrine, and campesterol also exhibited a lower docking energy than memantine and Risperdal. *Phellodendri chinensis cortex* was shown to contain most of these compounds. (Table 6 and Figure 6).

### TABLE 6: The docking results of the active ingredients with DRD2 and HTR2A
### Table 1: Binding Energies of Membrane Binding Sites

| Name          | DRD2 (PDB ID:6CM4) binding energy (Kcal/mol) | HTR2A (PDB ID:6A93) binding energy (Kcal/mol) |
|---------------|---------------------------------------------|---------------------------------------------|
| Memantine     | -6.72                                       | -6.02                                       |
| Risperdal     | -7.71                                       | -7.9                                        |
| Beta-sitosterol| -9.58                                       | -8.2                                        |
| Stigmasterol  | -9.17                                       | -8.9                                        |
| Chelerythrine | -8.1                                        | -8.12                                       |
| Campesterol   | -7.37                                       | -8.67                                       |
| Berberine     | -7.87                                       | -7.61                                       |
| Oroxylin a    | -7.38                                       | -6.42                                       |
| Acacetin      | -7.31                                       | -5.8                                        |
| Sudan III     | -6.87                                       | -6.95                                       |
| Baicalein     | -6.7                                        | -6.0                                        |
| Kaempferol    | -6.33                                       | -5.49                                       |
| Wogonin       | -5.68                                       | -5.95                                       |
| Quercetin     | -5.82                                       | -5.04                                       |
| Paniculn      | -5.53                                       | -5.74                                       |
| Coptisine     | -                                           | -                                           |
| Rutaecarpine  | -                                           | -                                           |
| Fumarine      | -                                           | -                                           |

Note: "-" indicates that the result has not been calculated.

### 4. Discussion

TCM plays an important role in medical diagnosis and treatments. Based on the TCM theory, Chinese formulas contain a mixture of herbs, combined based on the following combination principle; "monarch (Jun), minister (Chen), assistant (Zuo), and guide (Shi)" meaning that herbs play primary, secondary, auxiliary, or harmonic roles, respectively[17]. Primary herbs are substances that provide the main therapeutic thrust. Secondary herbs enhance or assist the therapeutic actions of the primary. The rest have the following functions: treat accompanying symptoms, moderate the harshness or toxicity of the primary ones, guide the medicine to the proper organs, or exert a harmonizing effect [18]. In HLJDD, *Coptidis rhizoma* plays the monarch role, *Scutellariae radix* plays the minister role while *Phellodendri chinensis cortex* and *Gardeniae fructus* play the assistant and guide roles, respectively. However, this combination is not suitable for treating BPSD. We studied drugs from the molecular perspective, and proposed a novel method for testing the combination of formulas. We found that *Scutellariae radix* and *Phellodendri chinensis cortex* are the principal herbs, while *Coptidis rhizoma* and *Gardeniae fructus* are the assistant herbs.

In AD, the abnormal accumulation of amyloid-β released from amyloid precursor protein and neuroinflammation are its partially pathologic hallmarks. Amyloid-β accumulation also causes indirect injuries to neurons by inducing neuroinflammation[19]. Microglia, the resident innate immune cells in the brain, are important in AD immune responses. They act as sentinel and protective cells, but may become inappropriately reactive in AD to drive neuropathology[20]. With advances in age, microglia exhibit enhanced sensitivity to inflammatory stimuli, similar to that observed in brains with ongoing neurodegeneration[21]. The lipopolysaccharide (LPS), a gram-negative bacterial endotoxin released from the cell wall, mediates inflammation in the body, involving in regulating the expression of potential inflammatory factors[22]. Studies have linked schizophrenia with neuroinflammatory conditions and microglia, which have been correlated to the pathogenesis of schizophrenia. Neuroinflammatory changes observed in schizophrenia involve abnormal astrocyte functions[23]. In our study, *Scutellariae baicalensis* was shown to play anti-inflammatory roles, including regulating neuroinflammatory responses, mediating lipopolysaccharide-mediated signaling pathways, cellular response to interleukin-6, and regulation of interferon-α production during BPSD treatment. *Gardeniae fructus* was shown to regulate amyloid-beta formation in BPSD therapy.

Smooth muscle cell proliferation, especially vascular smooth muscle cells, are essential during cell growth or injury[24]. Blood vessels with vascular smooth muscle cells play an important role in normal brain functions. Apart from supplying adequate blood, they help maintain its structural integrity and function. Shortages in cerebral blood flow and blood-brain barrier dysfunction are early findings in neurodegenerative disorders. Cerebral blood flow shortage, impaired cerebrovascular reactivity, and impaired hemodynamic responses are increasingly prevalent in the early stages of AD[25]. Platelets, critical blood flow factors, are anucleate blood cells whose principal function is to stop bleeding by forming aggregates for hemostatic reactions. Platelet aggregates are also involved in pathological thrombosis and play an essential role in inflammation[26]. Nitric oxide (NO) is a small free radical molecule with an endothelium-derived relaxing factor. Adequate levels of NO in the vascular endothelium are critical for regulating blood flow and vasodilation. Moreover, NO plays a vital neuronal signaling role[27]. Cadmium, a metal that resembles zinc and calcium, is also crucial for neuronal
signaling. Cadmium exposure is associated with neurodegenerative diseases such as AD. It can alter neurotransmitters' release, cause oxidative stress, damage the mitochondria, and induce apoptosis[28]. In our study, *Scutellariae radix* was shown to positively regulate smooth muscle cell proliferation, endothelial cell proliferation, and blood vessel endothelial cell migration; *Coptidis rhizoma* was shown to mediate cellular responses to cadmium ion; *Phellodendri chinensis cortex* was shown to regulate platelet activation while *Gardeniae fructus* regulated the nitric oxide biosynthetic process.

Macroautophagy is an evolutionarily conserved dynamic pathway that functions primarily in a degradative manner. Various diseases are associated with macroautophagic dysregulation. Macroautophagy plays a critical role in cellular homeostasis. Insufficient or excessive macroautophagy can seriously compromise cell physiology[29]. *Coptidis rhizoma* was shown to negatively regulate macroautophagy while *Phellodendri chinensis cortex* regulated glial cell apoptosis.

Studies have documented that Nicotine might be involved in the pathophysiology of psychosis. Smoking is correlated with depression. In animal models, Nicotine exhibited anxiolytic properties. Depressed people are more likely to smoke and more likely to develop severe depressive episodes upon smoking cessation. Nicotine has also been observed to exhibit similar cognitive improvements in AD patients[30]. However, the relationship between smoking and AD has not been clearly elucidated[31]. In the study, *Coptidis rhizoma* and *Phellodendri chinensis cortex* can respond to nicotine.

It has been documented that serotoninergic, dopaminergic, and cholinergic systems are involved in BPSD pathogenesis, and the roles of HTR2A and DRD2 as therapeutic targets are evident[15]. We used molecular docking to determine the potential active ingredients that exhibited good binding activities to DRD2 and HTR2A. The best-docked compound was beta-sitosterol. The free binding energy of beta-sitosterol with DRD2 and HTR2A was -9.58 kcal/mol, -8.2 kcal/mol, respectively. Stigmasterol, chelerythrine, and campesterol also exhibited good binding activities. The active ingredients of *Phellodendri chinensis cortex* were found to be beta-sitosterol, Stigmasterol, chelerythrine, and campesterol. It is the only herb containing these five ingredients.

The TCM theory verifies our results. Triple energizers in TCM theory mean upper, middle, and lower energizers. They are the birth and channel to run for Qi, blood, thin, thick fluids, and essence. Moreover, they also contact five Zang-organs and six Fu-organs. *Scutellariae radix* affects the upper energizer, which consists of the brain and heart; *Phellodendri chinensis cortex* affects the lower energizer, which is the kidney and liver while *Coptidis rhizoma* influences the middle energizer that consists of the spleen and stomach. Kidney essence deficiency is a primary syndrome differentiation of AD in TCM theory. Due to the imbalance between yin and yang of liver functions, "Liver re" is the largest contributor to BPSD[32 33]. *Phellodendri chinensis cortex* acts on the lower energizer to purge the liver fire. "Su Wen" puts forward that "the mind is the monarch's official, and the gods come out of it." In the compendium of *Materia Medica*, Shizhen Li of the Ming Dynasty proposed that "the brain is the house of primordial God." *Scutellariae radix* works on the heart and brain, belonging to the upper energizer. In conclusion, based on the TCM theory, *Scutellariae radix* and *Phellodendri chinensis cortex* are HLJDD's primary herbs.

5. Conclusions

The therapeutic value of natural products in the management of BPSD has increased due to their clinical efficacy and insignificant side effects. Different types of compounds have been reviewed for their biological activities. Our results showed that *Scutellariae radix* has more molecular targets and biological processes involved in BPSD while *Phellodendri chinensis cortex* exhibited more well-docked compounds: poriferast-5-en-3beta-ol (beta-sitosterol), Stigmasterol, chelerythrine, and campesterol, which have a lower affinity for DRD2 and HTR2A. *Scutellariae radix* and *Phellodendri chinensis cortex* were found to have the primary compounds for treating BPSD. *Scutellariae radix* plays an anti-inflammatory role while *Phellodendri chinensis cortex* regulates apoptotic processes and response to nicotine. They both regulate blood vessels. *Coptidis rhizoma* and *Gardeniae fructus* play the assistant role in BPSD, and are involved in neuronal signaling.

### Abbreviations

AD: Alzheimer's disease; BPSD: Behavioral and psychological symptoms in dementia; HLJDD: HuanglianJiedu decoction; DRD2: Dopamine D2 receptor; HTR2A: 5-hydroxytryptamine receptor 2A; TCM: traditional Chinese medicine; EPS: extrapyramidal severe side effects; TCMSp. TCM systems pharmacology database and analysis platform; OB: oral bioavailability; DL: drug-likeness; HL: half-life; STITCH: search tool for interactions of chemicals database; GO: Gene Ontology; D-CS: BPSD correlation score; NMDA: N-Methyl-D-aspartic acid; LPS: Lipopolysaccharide; NO: nitric oxide.

### Declarations

#### Data Availability

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

#### Competing interests

The authors declare no competing financial interest.

#### Authors’ contributions
Suya Ma wrote the manuscript. XW constructed the pharmacological networks. Jing Shi revised the manuscript. All authors were responsible for reviewing data. All authors read and approved the final manuscript.

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Figures
Figure 1

Schematic presentation of the method to discover the novel combination of HLJDD in treating BPSD.
Figure 2

Schematic presentation of Scutellariae radix’s potential mechanism in treating BPSD. a The “compounds-targets-BPSD” network of Scutellariae radix. This systematic approach successfully revealed 24 key protein targets related to BPSD: APOE ((BPSD correlation score, D-CS): 156.68), TNF (D-CS: 114.77), SOD2 (D-CS: 114.23), IL 6 (D-CS: 105.12), BDNF (D-CS: 104.54), IL 10 (D-CS: 86.21), VEGFA (D-CS: 72.66), AKT1 (D-CS: 66.45), CCL2 (D-CS: 66.37), MAPK1 (D-CS: 52.1), PLAU (D-CS: 41.02), CASP3 (D-CS: 37.17), ICAM1 (D-CS: 37.08), PTGS2 (D-CS: 35.32), NOS1 (D-CS: 32.33), MMP9 (D-CS: 30.39), MYC (D-CS: 30.15), IL 13 (D-CS: 29.05), MAPK3 (D-CS: 26.17), HMGB1 (D-CS: 23.14), JUN (D-CS: 22.83), STAT1 (D-CS: 20.14), TNFSF11 (D-CS: 18.98), CYP3A4 (D-CS: 17.31). b GO biological processes analysis of Scutellariae radix. Scutellariae radix’s key protein targets involved 156 biological processes, such as positive regulation of smooth muscle cell proliferation, lipopolysaccharide-mediated signaling pathway, and neuroinflammatory responses.