

Research Progress on Classical Traditional Chinese Medicine Jieyu Pills in the Treatment of Depression

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Abstract: Depression is a common clinical psychological disease, which is called “yu zheng” in traditional Chinese medicine (TCM). TCM has a long history in the treatment of depression (yu zheng), which has unique advantages. Jieyu pill (JYP), a classical TCM formula, has been widely used for treating depression because of its clear clinical efficacy, low side effects, and high compliance. In this review, we systematically introduce recent clinical and animal experimental studies on JYP and depression, and review the pharmacological mechanism and active ingredients of JYP, as well as its clinical application in depression therapy. This systematic review provides a deep understanding of TCM prescriptions, pharmacological mechanisms, and disease–medicine interactions, and lays the foundation for developing new treatments for depression.

Keywords: Jieyu pill, depression disorder, yu zheng, pharmacology, active ingredient

Introduction

Depression disorder is one of the most common psychological diseases in a clinical context. According to the International Classification of Diseases (ICD-11) published by the World Health Organization (WHO), depression is characterized by a lack of pleasure, accompanied by impairments in cognitive, behavioral, and autonomic functions, which seriously affect the patient's social function.¹ According to statistics released by the WHO in 2017, there are 322 million depressive patients globally, with an overall prevalence of 4.4%. The prevalence rates in women and men are 5.1% and 3.6%, respectively. Depressive disorder is a major cause of disability globally and a major factor in the global disease burden.² However, less than half of patients globally receive anti-depression therapy, and there are still great difficulties and challenges regarding the diagnosis and treatment of depression.³

Traditional Chinese medicine (TCM) is an experience-based medicine that has been developed in China over thousands of years. After repeated clinical practice, a TCM formula is established, which is typically composed of multiple drugs and can act on multiple organs and targets. This multichannel treatment method is compatible with the multifactorial pathological mechanism of depression. A variety of TCM formulas have been used clinically in the treatment of depressive disorders. Meta-analysis has shown that the treatment of depressive disorders with Chinese medicine is superior to a placebo in terms of improving symptoms. Its effectiveness is similar to that of Western medicine antidepressants, but with a lower incidence of adverse events.⁴

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Depression and Yu Zheng

In TCM, it is believed that a depressed mood is caused by emotional trauma, and is classified as “yu zheng.” In the “Jingyue Quanshu,” people believed that all diseases originated from five qi stasis, which emphasized the importance of “yu zheng” in human diseases. Previous studies found that the four common symptoms of depression disorder are 1) liver qi stagnation, 2) liver stagnation and spleen deficiency, 3) heart and spleen deficiency, liver stagnation and qi stagnation, and 4) liver and kidney yin deficiency, with liver qi stagnation being the most common.⁵ In TCM, it is believed that “yu zheng” is mainly caused by stagnation of liver qi. The disease is located in the liver and closely associated with the spleen, kidney, and heart. Therefore, the treatment should be based on the liver, which should relieve the depression of the liver and ventilate the qi and blood, and make the functions of the viscera, the whole body, and the organs stable and orderly, so that the emotions can be smoothed.

JYP is a pure Chinese medicine formula refined by modern science and technology. As a commercial drug, JYP is widely used in clinic. It was developed on the basis of ancient formulas, namely, Xiaoyao decoction and Ganmai Dazao decoction, and is composed of *Paeoniae Radix Alba*, *Radix Bupleuri*, *Angelicae Sinensis Radix*, *Curcumae Radix*, *Poria cocos* (Schw.) Wolf., and *Jujubae Fructus*. *Paeoniae Radix Alba* nourishes the blood and soothes the liver, while *Radix Bupleuri* soothes the liver and regulates qi. *Curcumae Radix* not only effects on the qi but also on the blood, which can relieve qi stasis and cool the clearing heart. It is more effective at nourishing the blood and promoting blood circulation in combination with *Angelicae Sinensis Radix*. Four drugs constitute the classic prescription Xiaoyao decoction, which is used to treat fullness of chest hypochondrium, and depression. *Poria cocos* (Schw.) Wolf. and *Jujubae Fructus* have the effects of nourishing the heart, relieving depression and removing anxiety, and treating palpitations, insomnia, and dreaminess. JYP is a brown to tan water pill, slightly bitter, weighing 1 gram per 15 pills. When the six drugs are used together, JYP has the greatest therapeutic effect on “yu zheng” (depression disorder) in biomedicine.

Pharmacological Studies on the Active Ingredients of the Six Chinese Medicines Comprising JYP *Paeoniae Radix Alba* (PRA)

PRA is the dried root of *Paeonia tacts lora* Pall., it has the functions of nourishing the blood and regulating menstruation,

condensing the yin and antiperspirant, softening the liver and relieving pain, and calming the liver and yang. It is commonly used for blood deficiency, irregular menstruation, spontaneous sweating, night sweats, flank pain, abdominal pain, limb pain, headache, and dizziness.^{6,7} Previous studies showed that PRA could be used for anti-inflammatory effects,⁸ immune regulation,⁹ treatment of depression^{10,11} and anemia,¹² promotion of peripheral nerve regeneration,¹³ and treatment of viral infections.¹⁴

Modern studies of pharmacological mechanisms have found that the main active components of PRA include paeoniflorin, paeonol, paeonin, benzoylpaeoniflorin, albi-florin, oxypaeoniflorin, paeoniflorigenone, benzoic acid, β -sitosterol, and gal-lotannin. Paeoniflorin is the main pharmacological component of PRA. It has been reported to have neuroprotective effects in a transgenic mouse model of Alzheimer’s disease (AD),¹⁵ can influence the prognosis of chronic heart failure (CHF),¹⁶ ameliorate antipsychotic drug-induced side effects,¹⁷ attenuate early brain injury through reducing oxidative stress and neuronal apoptosis after subarachnoid hemorrhage in rats,^{18,19} and exert antitumor effects,²⁰ protective effects on acute cerebral infarction,²¹ and anti-inflammatory and immunoregulatory effects,²² as well as promote neurogenesis in the hippocampal dentate gyrus of depressive-like rats.²³

Radix Bupleuri (RB)

RB is an umbelliferous plant, which is mostly dug up in spring and fall. It is commonly used as an antidote. It is bitter and slightly cold, belonging to the channels of liver and gall bladder. RB has the effects of reconciling super-ficies and interior, complementing qi, and soothing the liver. It is used to treat liver qi stagnation, chest and rib pain, anal prolapse, uterine prolapse, and irregular menstruation. In recent years, research on the application of RB has mainly focused on its use against depression,²⁴ for inhibiting cancer growth and metastasis,²⁵ anti-hepatitis B virus (HBV) effects,²⁶ antioxidative, anti-inflammatory, and hepatoprotective effects,²⁷ antimicrobial, antiviral, hepatoprotective, neuroprotective, and immunomodulatory effects,^{28,29} anti-epileptic effect,³⁰ and its use for treating AD.³¹

Although there is an extensive range of clinical applications of RB, recent research has mainly focused on its anti-depressant effect. Through the study of the pharmacological mechanism of RB, it has been found that its main active ingredients include saikosaponin, sterols, volatile oils (chailuol, eugenol), fatty acids (oleic acid, linoleic acid, palmitic

acid, stearic acid), and polysaccharides. Among these, the main ingredient is saikosaponin. Saikosaponin has the following positive effects: antitumor³² and antiviral activities,³³ regulation of triglycerides,³⁴ antidepression effects,³⁵ the prevention and treatment of atherosclerosis, improvement of memory deficits,³⁶ antiepileptic effects,³⁷ the suppression of inflammatory responses³⁸ and reduce depressive, anxiety-like behavior in chronic corticosterone-treated mice [10.1186/s12906-018-2186-9].

Angelicae Sinensis Radix (ASR)

ASR is the dried root of *Umbelliferae Angelica sinensis* (Oliv) Diels. In terms of its properties, it is sweet, spicy, and warm, belonging to the channels of liver, heart, and spleen. The main functions of ASR include nourishing the blood, promoting blood circulation, regulating menstruation and analgesia, moisturizing and smoothing the intestines, and relieving abdominal pain due to cold deficiency and numb skin. Recent studies have also found that ASR can be used to treat idiopathic pulmonary fibrosis,³⁹ depression,⁴⁰ and multiple sclerosis.⁴¹ It also has the effects of ameliorating memory deficiency⁴² and promoting axon regeneration after ischemic brain injury,⁴³ as well as exerting anti-inflammatory⁴⁴ and neuroprotective effects,⁴⁵ and promoting synaptic plasticity during cognitive recovery.⁴⁶

Studies of its pharmacological mechanisms have confirmed that ASR has many active ingredients, including butylidenephthalide, β -pinene, α -pinene, camphene, p-cymene, β -phellandrene, myrcene, allo-ocimene, 6-n-butyl-cycloheptadiene-1, acetophenone, β -bisabolene, isoacoraene, acoradiene, chamigrene, α -cedrene, and bergapten. Among these, butylidenephthalide is the most studied and widely used. Studies have shown that butylidenephthalide can prolong the lifespan and attenuate motor neuron loss in a superoxide dismutase 1 (SOD1) mouse model of amyotrophic lateral sclerosis (ALS),⁴⁷ act in adjuvant therapy of malignant human gliomas,⁴⁸ rehabilitate the neurovascular unit in rats after photothrombotic stroke,⁴⁹ exhibit therapeutic effects in a mouse model of Parkinson's disease (PD),⁵⁰ protect against neurotoxicity in spinocerebellar ataxia type 3,⁵¹ attenuate AD-like cytopathy in Down syndrome,⁵² and prevent inflammation-mediated neurotoxicity.⁵³

Curcuma Radix (CR)

CR is the dried root of *Curcuma rnenyujin* Y, H. Chen et C. Ling. It is usually dug up after the stems and leaves wither in winter. In terms of the properties of CR, it is

spicy, bitter, and cold, belonging to the channels of liver, heart, and lungs. The effects of CR include: promoting blood circulation and relieving pain, relieving qi stagnation, clearing the heart, and cooling the blood. It can be used for chest obstruction with pain, epilepsy, amenorrhea, and oligomenorrhea. In addition, CR has anti-inflammatory and antinociceptive,⁵⁴ antiepilepsy,⁵⁵ antitumor,⁵⁶ and antidepression effects,⁵⁷ while also countering autoimmune liver disease⁵⁸ and atherosclerosis, exerting cardioprotective effects,⁵⁹ and assisting in the treatment of AD.⁶⁰

It has been reported that CR root contains curcumin, aromatic curcumin, gingerene, cressene, cypressene, eucalyptol, borneol, camphor, and curcumin. Among these, research on curcumin has been most intensively performed, and curcumin is currently considered to have the highest medicinal value among these components. Curcumin has been used for the adjuvant treatment of depression,⁶¹ shown to exert beneficial effects on depression and anxiety in diabetic patients,⁶² and to improve unpredictable chronic mild stress-induced depression and memory deficits.⁶³ In addition, curcumin was reported to prevent or delay the onset of various neurological diseases, such as AD, PD, Huntington's disease (HD), multiple sclerosis, and ALS.⁶⁴

Poria cocos (Schw.) Wolf (PCW)

PCW is the dried sclerotia of the fungus *Poria cocos* (Schw.) Wolf in the Polyporaceae family. In terms of the properties of PCW, it is sweet and light, belonging to the heart, lung, spleen, and kidney channels. Its pharmacological effects include diuresis and dampness, strengthening the spleen, and calming the heart. It is mainly used to treat edema and oliguria, sputum drinking and dizziness, spleen deficiency, restlessness, convulsions, and insomnia. Clinically, PCW is mainly used for treating renal fibrosis,⁶⁵ osteoporosis,⁶⁶ malignant tumors,⁶⁷ cerebral ischemia/reperfusion injury,⁶⁸ depression,⁶⁹ fatty liver,⁷⁰ diabetes,⁷¹ and AD.⁷²

PC is abundantly available, and its pharmacological effects are remarkable. So far, the main chemical components that have been separated from PC include poria glycans, pachymic acid, as well as sterols, choline, adenine, lecithin, and histidine acid. The pharmacological effects of pachymic acid include antitumor activity,⁷³ improving learning and memory impairment,⁷⁴ protecting against cerebral ischemia/reperfusion injury,⁶⁸ ameliorating renal failure,⁷⁵ improving survival and attenuating acute lung injury,⁷⁶ improving sleep,⁷⁷ and exerting anti-inflammatory⁷⁸ and

antihyperglycemic effects.⁷⁹ In addition, pachymic acid has clear antidepressant and anxiolytic effects.^{80,81}

Jujubae Fructus (JF)

JF belongs to the genus *Zizyphus* of the Rhamnaceae family. It is sweet in taste and warm, belonging to the spleen and stomach channels. JF has the functions of supplementing qi, nourishing the blood, calming the mind, and relieving drug resistance. It exerts optimal effects for treating allergic purpura, anemia, hypertension, acute and chronic hepatitis, and cirrhosis, as well as preventing blood transfusion reactions. JF contains triterpenoid compounds and cyclic adenosine phosphate, having strong anticancer and antifatigue effects. JF also has the effect of reducing damage due to toxic substances in the liver, while the flavonoids in JF have sedative and blood-pressure-lowering effects.

JF mainly contains organic acids, triterpene glycosides, alkaloids, and flavonoids. These organic acids include betulinic acid and oleanolic acid; the triterpene glycosides include maslinic acid-3-O-trans-p-coumarinyl ester and maslinic acid-3-O-cis-p-coumarinyl ester; the alkaloids include stepharine and n-nornuciferine; and the flavonoids include 6,8-di-C-glucosyl-2(S)-naringenin, 6,8-di-C-glucosyl-2(R)-naringenin, and rutin. Betulinic acid is one of the main effective ingredients of JF. Studies have shown that it has therapeutic effects on various diseases, such as influenza virus infection,⁸² glioblastoma,⁸³ ischemic stroke,⁸⁴ and a variety of malignant tumors.^{85,86} In addition, betulinic acid has unique effects on improving AD and combating anxiety/depression.^{87,88}

The Clinical Application of JYP in the Treatment of Depression

In recent years, with the deepening of people's understanding of TCM, JYP and its modified versions have been widely used in the treatment of depression and related psychological disorders. JYP was shown to be effective in treating depression, and studies have reported that the rate at which it was effective was 78.8%, which is equivalent to the efficacy of treatment with the Western medicine maprotiline. JYP can also significantly improve patients' Hamilton Depression Rating Scale (HAMD) score, Self-rating Scale for Depression (SDS) score, Self-rating Scale for Anxiety (SAS) score, and Clinical Global Impression (CGI) score. In addition, Shen et al showed through randomized controlled trials that JYP is as

effective as maprotiline in the treatment of depression, but has fewer side effects.⁸⁹ Adding JYP to Western medicine in the treatment of depression could thus achieve good results. Liu et al collected and followed up 32 patients with refractory depression (RD) in the form of yin deficiency inner heat syndrome (YDIHS), treated with JYP and paroxetine, and evaluated their HAMD and Hamilton anxiety scale scores at the second, fourth, and eighth weeks. They found that JYP combined with paroxetine was superior to the use of paroxetine alone.⁹⁰ Moreover, in a comparative study of the efficacy of JYP combined with sertraline versus sertraline alone in the treatment of depression, Qu et al found that the improvement of depressive symptoms was more pronounced in patients treated with JYP. Moreover, the levels of the inflammatory factors interleukin-2 (IL-2), IL-6, tumor necrosis factor- α (TNF- α), and IL-1 β were significantly reduced, while 5-serotonin (5-HT), norepinephrine (NE), and dopamine (DA) levels were significantly increased in the serum of patients receiving JYP treatment, suggesting that JYP combined with sertraline could effectively improve the depressive state of patients and promote the secretion of monoamine neurotransmitters. Furthermore, Chen et al performed a study including 116 patients with depression, to whom JYP combined with Shugan Jieyu capsule therapy was applied. Through a 6-week follow-up study of these patients, it was found that the depressive symptoms were significantly alleviated in patients receiving JYP treatment, which did not increase the incidence of adverse effects. The study also suggested that JYP could improve the quality of sleep of patients with depression.⁹¹ JYP combined with citalopram can improve the symptoms of patients with RD, and can significantly increase the serum 5-HT, NE, and brain-derived neurotrophic factor (BDNF) levels in patients, suggesting that the mechanism of JYP to improve depressive symptoms may be related to the regulation of monoamine transmitter levels and the activation of BDNF expression. In addition to improving depressive symptoms, JYP could also improve stroke symptoms and the ability to perform daily living activities among patients with post-stroke depression, so JYP is also recommended for such patients.⁹²

In summary, these clinical studies have shown that JYP alone or combined with other TCM or Western medicines is effective in treating depression, and has fewer side effects than conventional drugs. The mechanism by which JYP acts in the treatment of depression is relatively complex. Clinical studies performed to date have found

that it may rely on increasing 5-HT, NE, and DA levels. From the dialectical perspective of TCM, JYP mainly treats depressive patients by improving liver qi stagnation syndrome, liver stagnation, and spleen deficiency syndrome. Next, we review the possible mechanisms by which JYP acts in treating depression.

The Pharmacological Mechanism of JYP in the Treatment of Depression

With the increasing clinical application of JYP, research on its pharmacological mechanism has also received more and more attention. Wang et al suggested that JYP has an ameliorative effect on post-stroke depression in rats via modulating BDNF levels, cannabinoid receptors, and corticotrophin-releasing factor in ventral tegmental area-nucleus accumbens tissue.⁹³ Paeoniflorin, an active ingredient of PRA, can improve the depression-like behavior caused by chronic stress. This antidepressant effect may occur by regulating the functional activity of the hypothalamic-pituitary-adrenal (HPA) axis and increasing BDNF levels in the brain.⁹⁴ It was reported the paeoniflorin could also ameliorate depressive-like behavior by decreasing the degree of neuronal damage in the hippocampus of model rats. In addition, paeoniflorin was reported to exert a neuroprotective effect by modulating the ERK-CREB signaling pathway in rats with chronic unpredictable mild stress-induced hippocampal damage.⁹⁵ Pharmacodynamic tests showed that paeoniflorin had significant antidepressant activity through its metabolism into benzoic acid via gut microbiota enzymes, which might exert antidepressant effects by passing through the blood-brain barrier into the brain.⁹⁶ Saikosaponin could also effectively improve lipopolysaccharide-induced inflammation-related depressive-like behaviors by inhibiting microglia activation and neuroinflammation.³⁵ Moreover, Chao et al suggested that saikosaponin could ameliorate depression-like behaviors in rats by downregulating nuclear factor- κ B (NF- κ B) and miR-155, and upregulating fibroblast growth factor 2 (FGF2).⁹⁷ The results of Gong et al demonstrated that ASR could significantly improve chronic unpredictable mild stress-induced depressive symptoms, hematological anomalies, and hypoxia symptoms by modulating energy metabolism and inhibiting the expression of pyruvate dehydrogenase lipoamide kinase isozyme 1 and lactate dehydrogenase A.⁴⁰ The butyridenephthalide in ASR could regulate the nuclear factor E2 related factor

2 and NF- κ B pathway, produce anti-inflammatory effects, and improve lipopolysaccharide-induced depression-like behavior.⁹⁸ Curcumin is widely used as an anti-inflammatory agent and has the potential to combat depression. It exerts anti-depression effects by inhibiting P2X7R expression, which then deactivates the Ca^{2+} channel-mediated inflammatory response associated with the exacerbation of depression.⁹⁹ Naqvi et al reported that curcumin supplementation significantly attenuated unpredictable chronic mild stress-induced depression, decreased the load of unpredictable chronic mild stress propagated oxidative stress by improving antioxidant enzyme activities.⁶³ Curcumin also attenuated IL-1 β -induced neuronal apoptosis, which may be related to depression-like behavior in stressed rats.¹⁰⁰ Moreover, curcumin effectively decreased the levels of pro-inflammatory cytokines (TNF- α , IL-1 β , and IL-6) and suppressed NF- κ B activation, while also inhibiting stress-induced P2X7R/NLRP3 inflammatory axis activation, along with reducing the transformation of pro-IL-1 β to mature IL-1 β , thereby relieving the depression-like state through inhibiting the NLRP3 inflammatory pathway.¹⁰¹

This review of previous studies clearly shows that various active ingredients in JYP can produce different therapeutic effects through different targets in depression therapy. Different ingredients in JYP may increase the levels of monoamine neurotransmitters in the brain, adjust the HPA axis, and produce anti-inflammatory effects and other regulatory effects on energy and substance metabolism pathways to synergistically exert antidepressant effects, suggesting the broad potential of JYP in the treatment of depression.

The Active Compounds of JYP in the Treatment of Depression

In TCM, the treatment of depression is usually based on an overall analysis of the illness and the patient's condition, in-depth analysis of the etiology and pathogenesis of depressive disorder, correction and selection of prescriptions during repeated consultations, and ultimately relieving the depressive symptoms. The antidepressant effect of JYP is a synergistic effect of multiple effective ingredients, with the therapeutic effect occurring through the synergistic activities of multiple drugs. This therapeutic effect thus involves the characteristics of multiple ingredients, multiple targets, and multiple pathways. As such, it is difficult to study the

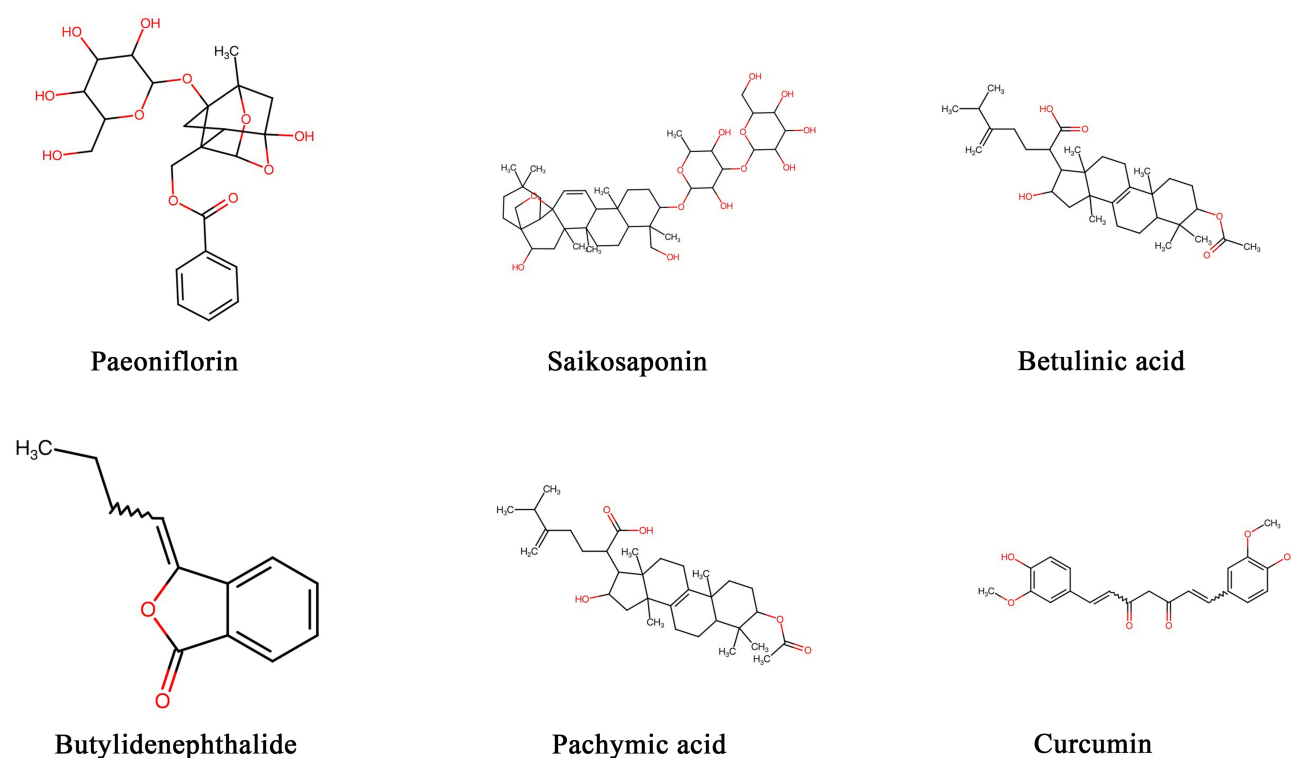


Figure 1 The 2D structures of effective biomarkers in JYP (JYP, Jieyu pill).

pharmacological mechanism of TCM formula comprehensively by traditional experimental methods.

Network pharmacology is a new field of study based on the theory of systems biology, which analyzes networks of biological systems and selects specific signal nodes for the design of multiple targeted drugs. Basing on the parameters of distribution, absorption, metabolism and excretion, we first screened the active ingredients of JYP by

searching the pharmacological database of the traditional Chinese medicine system platforms (TCMSP) (<http://www.tcmspw.com/>). A total of six active ingredients in JYP were identified, including paeoniflorin, saikosaponin,

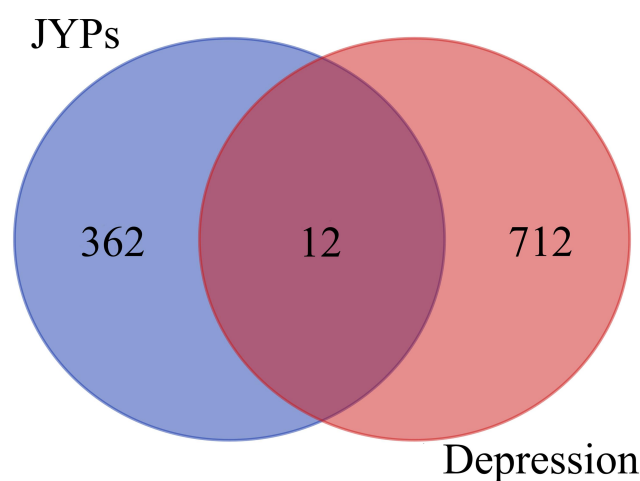


Figure 2 A total of 12 targets of both JYP and depression were identified.
Abbreviations: JYP, Jieyu pill; TCM, traditional Chinese medicine.

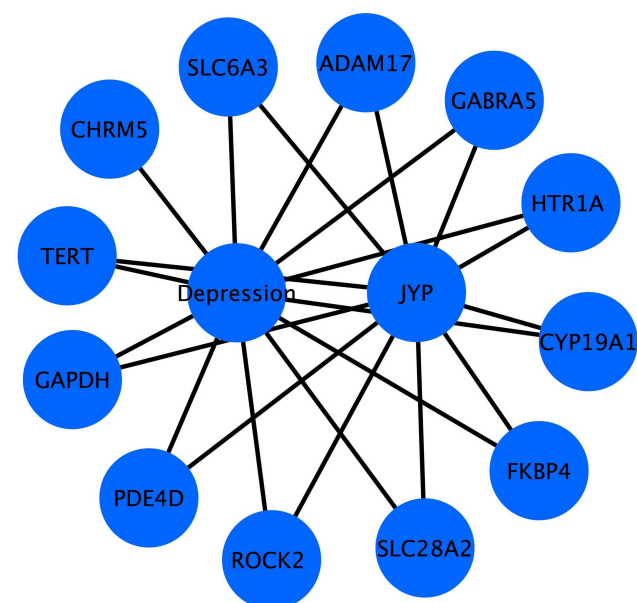


Figure 3 A total of 12 targets were used to establish the regulatory network in Cytoscape.
Abbreviation: JYP, Jieyu pill.

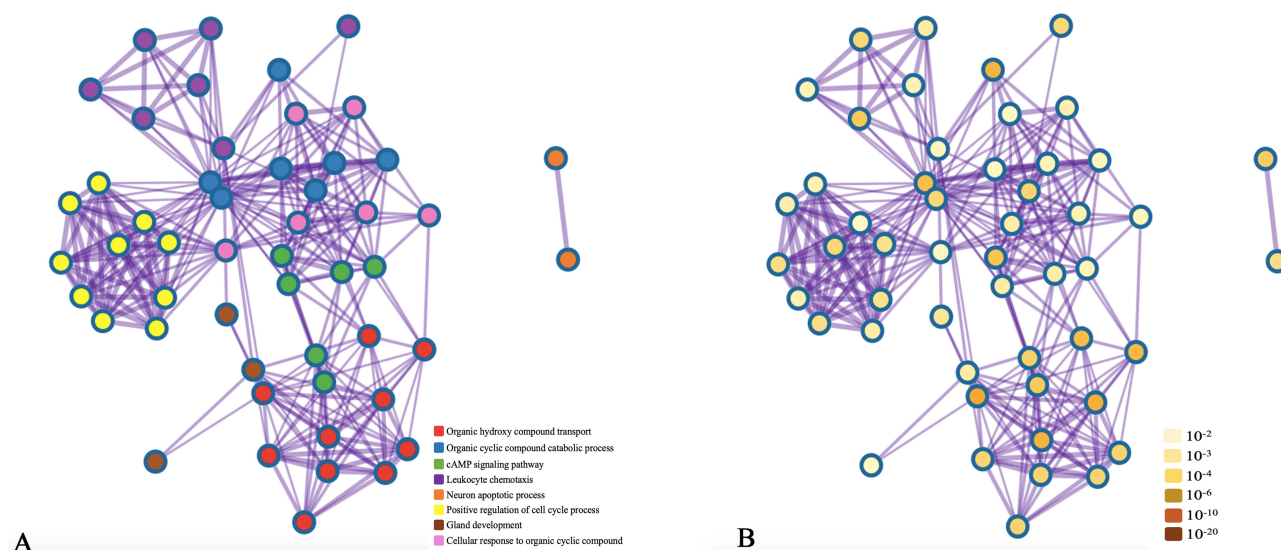


Figure 4 Network of enriched terms: (A) colored by cluster ID, where nodes that share the same cluster ID are typically close to each other; (B) colored by *p*-value, where terms containing more genes tend to have a more significant *p*-value.

butylidenephthalide, curcumin, pachymic acid and betulinic acid. The 2-D structure and the Canonical SMILES of eight effective biomarkers in JZG were obtained from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) (Figure 1). The Swiss Target Prediction database (<http://www.swisstar.getprediction.ch/>) and Lab of Systems Pharmacology (<http://www.tcmsp.w.com/>) were used to screen the targets of the active biomarkers in JYP. The targets of depression were obtained from the Therapeutic Targets database (<http://bidd.nus.edu.sg/group/cjttd/>) and the OMIM database (<http://omim.org/>).

Ultimately, 362 target genes of JYP and 712 target genes of depression were identified; as a result, 12 collective targets of depression and JYP were obtained (Figure 2). Metascape (<http://metascape.org>) provides automated meta-analysis tools to understand common and unique approaches in a set of orthogonal target discovery studies. It also supports BioGrid-based protein–protein interaction (PPI) analysis and interactive visualization of Gene

Ontology (GO) networks.¹⁰² The network of enriched terms was analyzed by Metascape (Figure 3) and the PPI was constructed by Cytoscape (Figure 4). The top eight clusters with representative enriched terms of JYP's actions on depression are shown in Table 1. We speculate that JYP may treat depression via these enriched pathways.

Conclusion and Prospects

Depression is a psychological disorder with a high prevalence rate, for which drug treatment is currently the main therapeutic method. Drug selection should be based on a variety of factors, including: treatment response to previous drugs; drug safety, tolerability, and adverse reactions; concomitant mental or physical illnesses; and pharmacological characteristics of the drugs. Western medicine antidepressants have significant therapeutic effects, but their safety, tolerance, and compliance are relatively poor. JYP was innovatively developed on the basis of a TCM prescription; it is mainly used for the

Table 1 Top eight Clusters with Their Representative Enriched Terms of JYPs on the Depression

GO	Category	Description	Count	%	Log10 (P)
GO:0015850	GO Biological Processes	Organic hydroxy compound transport	4	33.33	−5.19
GO:1,901,361	GO Biological Processes	Organic cyclic compound catabolic process	5	41.67	−4.68
GO:0030595	GO Biological Processes	Leukocyte chemotaxis	3	25.0	−3.79
GO:0051402	GO Biological Processes	Neuron apoptotic process	3	25.0	−3.68
GO:0090068	Canonical Pathways	Positive regulation of cell cycle process	3	25.0	−3.40
GO:0048732	GO Biological Processes	Gland development	3	25.0	−2.93
GO:0071407	GO Biological Processes	Cellular response to organic cyclic compound	3	25.0	−2.67

treatment of depression, upset, insomnia, and dreaminess caused by the stagnation of liver qi and restlessness. In clinical practice, it has been found that JYP has good clinical efficacy in the treatment of depressive disorders and accompanying symptoms. In combination with Western medicine antidepressants, it not only has a synergistic effect, but also reduces adverse reactions and has high compliance. Here, the effects of JYP on depression have been systematically reviewed from the perspectives of composition, animal experiments, pharmacological actions, effective components, and clinical applications. Through these studies, we hope to provide a comprehensive and profound understanding of the mechanism by which JYP acts on depression, and scientific guidance for JYP's wider clinical application.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

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