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REVIEW

Traditional Chinese Medicine Jiuwei Zhenxin Granules in Treating Depression: An Overview

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Abstract: Depression is known as "Yu Zheng" in traditional Chinese medicine (TCM). Jiuwei Zhenxin granules (JZG) is a type of TCM. According to TCM theory, it nourishes the heart and spleen, tonifies Qi, and tranquilizes the spirit, and may also has effects in the treatment of depression. Here, we systematically reviewed recent basic and clinical experimental studies of JZG and depression, including studies of the pharmacological mechanisms, active ingredients, and clinical applications of JZG in depression treatment. This review will deepen our understanding of the pharmacological mechanisms, drug interactions, and clinical applications of TCM prescriptions and provide a basis for the development of new drugs in the treatment of depression.

Keywords: Jiuwei Zhenxin granules, depression, Yu Zheng, pharmacological, effective substance

Introduction

Depression is a common affective mental disorder. Its primary clinical characteristics are persistent depression, pessimism, lack of interest in surroundings, sleep disorders, mental and cognitive delays, and even suicidal tendencies.[1] Modern medical research suggests that chronic diseases, genetic factors, social and environmental factors can induce depression.[2] For example, genetic factors can determine a person's susceptibility to depression, and environmental factors can trigger depression.[3] The pathogenesis of depression is still not fully understood, but it is generally believed to be related to changes in brain neurotransmitters such as γ-aminobutyric acid (GABA), estrogen levels, neuronal cell factors, and cell signal transduction.[4,5] In recent years, there have been many theories about the pathogenesis of depression, including the norepinephrine hypothesis, the dopamine hypothesis, the neurotrophic/regenerative hypothesis, and the neural plasticity pathway regulation theory. These theories have important significance for guiding the clinical treatment of depression.[6,7] Clinical practice has proven that many chemical drugs have beneficial therapeutic effects in depression, but they are also associated with adverse reactions, such as drowsiness and dystonia, and have shortcomings, such as a narrow antidepressant spectrum and a high rate of relapse.[8] Increasingly, studies show that traditional Chinese medicine (TCM) and its compounded preparations exhibit unique effects in the treatment of depression. Not only are there fewer adverse reactions associated with TCM preparations, but their effects are comparable to those of chemical drugs, and patients easily accept and are compliant with such treatment.[9,10]

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TCM is a general term that includes medicine and practices of the Han nationality, as well as the minority nationality in China. TCM reflects the Chinese people's understanding of life, health, and disease: it has a long history of use and incorporates unique theories and technologies. Jiuwei Zhenxin granules (JZG) are a classical Chinese medicine prescription that has been used in the prevention and treatment of various depressive, anxiety, and bipolar disorders in China.[11] JZG originated from Pingbu Zhenxin and was first recorded in Tai Ping He pharmacy prescriptions in the Northern Song Dynasty. In the 1990s, the formula was revised by TCM Professor TuYa of Beijing University and Professor Xiaolan Cui of the Institute of Pharmacology of the Chinese Academy of Sciences. The main functions of JZG are to nourish and regulate the heart and spleen, replenish Qi, tranquilize the mind, and replenish blood. It is mainly used for the treatment of anxiety and depression, insomnia and dreaminess, palpitations, anorexia, mental fatigue, dizziness, and sweating. Recently, studies have confirmed that JZG has a significant effect on depression. In this review, we highlight the recent studies noting the progress of JZG in treating depression in order to facilitate an understanding of the pharmacology of JZG and provide a basis for the development of novel drugs for the treatment of depression.

The Understanding of Depression According to Traditional Chinese Medicine

According to TCM theory, it is believed that the five internal organs (heart, liver, spleen, lungs and kidneys), the body and all the orifices form an organic whole. The essence of the five internal organs is the material basis of emotion (Table 1). The main causes of depression are loss of liver drainage, healthy spleen function, and Heart nourishment. Although the three organs of the liver, spleen, and heart are related, each has its own emphasis and plays a different role in the development of depression. Liver Qi stagnation is mostly related to Qi, blood, and fire; while food, wetness, and sputum are mainly related to the spleen; manifestations of Heart deficiency include a loss of nourishment in the Heart, insufficient blood supply, and deficiency in Heart yin. The initial symptoms of depression are related to Qi and blood. Therefore, the symptoms of Qi stagnation and blood stasis are very common in clinical practice. Therefore, depression is categorized as "Yu Zheng," which, in TCM, refers to a type of disease or syndrome caused by the blockage of the five internal organs due to emotional depression and Qi stagnation. Its name comes from the "Inner Canon"[12]

In TCM, it is believed that "Yu Zheng" is primarily caused by long-term emotional stress and liver Qi stagnation: this causes the internal organs to function inconsistently, leading to disorders of Qi and blood, as well as the heart, spleen, and liver. The pathogenesis of "Yu Zheng" in TCM is mainly due to emotional failure, which leads to Qi stagnation, Qi and blood Yin and Yang disorders, and visceral dysfunction, and the core pathogenesis is the blockage of the Qi mechanism. Zhu Danxi in the Yuan Dynasty first proposed the theory of "Six Yu", which divided "Yu Zheng" into six features: Qi stagnation, blood stagnation, phlegm stagnation, fire stagnation, Shi

Table 1 Summarizing the Theory of Five Internal Organs in Traditional Chinese Medicine

Five Internal Organs	Physiological Characteristics	Physiological Function	Corresponding Organ
Heart	Head of five internal organs	Dominate blood and vessel and govern the mind	Nervous system, cardiovascular system
Liver	Being the resolute viscera	Take charge storing blood and catharsis	Endocrine, hematopoietic, nervous, digestive and reproductive systems
Spleen	Preferring dryness to dampness	Govern transportation and transformation, dominate rise of the clear, dominate blood control	Digestion, hematopoiesis, muscles and immune system
Lungs	Governing coordinative activities of viscera	Dispersing and descending motion, dominating water movement, connecting all vessels	Respiratory and immune system
Kidneys	Dominate storage, viscus of fire and water	Store essential substances, govern growth, development and reproduction, control the metabolism of water, govern reception of qi	The basis of all organs

stagnation, and food stagnation. Hu et al believe that "Yu Zheng" is primarily dominated by Qi stagnation, with secondary influences of phlegm stagnation, cold coagulation, and food stagnation, leading to different aspects of heart, spleen, liver, and kidney deficiencies.

Shen jing shuai ruo, also known neurasthenia, which was introduced in China in the early 1900s and commonly understood by the Chinese to mean "neurological weakness". These words translate as a weakness of the channels carrying vital energy, or Qi, through the body.[13] Shen jing shuai ruo became widely used diagnostically by psychiatrists and other medical practitioners, who viewed it as a state determined by the interaction between an inherited neurotic tendency and environmental stress and by the 1980s, as many as 80% of psychiatric outpatients in mainland China were diagnosed as primarily "neurasthenic", and up to one-half of general and psychiatric Chinese outpatients sought treatment for self-diagnosed neurasthenia. This is still relevant and applicable today.[14]

In the worldwide, the use of herbal medicine to treat mental disorders that has increased markedly. Incorporating TCM into conventional medicine to treat depression has various benefits such as better accessibility, acceptability and lesser stigma.[14] There are also evidence-based herbal therapies that have shown promising results in clinical trials, when compared to standard Selective Serotonin Reuptake Inhibitors (SSRIs), such as St John's wort[15] and Curcuma longa, which is a major constituent of the ancient herbal medicine Xiao Yao San and has demonstrated antidepressant activity in clinical trials.[16] JZG, a classical Chinese medicine prescription, nourishes the Heart and spleen, supplements Qi, and calms nerves: it is the main prescription for anxiety and depression caused by deficiency of both the Heart and spleen. Clinically, it can be used to treat generalized anxiety disorder with heart and spleen deficiency syndrome, symptomatic thinking, incomprehension, insomnia and dreams, heart palpitations, loss of appetite and fatigue. However, patients with yin deficiency and fire excess should use JZG with caution. The formula is composed of nine kinds of Chinese herbal medicines: *Panax ginseng C.A. Mey, Ziziphus jujuba Mill, Schisandra chinensis (Turcz.) Baill, Smilax glabra Roxb, Polygala tenuifolia Willd, Corydalis yanhusuo (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.Su & C.Y.Wu, Asparagus cochinchinensis (Lour.) Merr, Rehmannia glutinosa (Gaertn.)* DC., and *Cinnamomum cassia (L.) J. Presl*. According to traditional medicine, *P. ginseng (PG)* and *S. glabra Roxb (SGR)* invigorate vital energy, strengthen the blood vessels and spleen, benefit the lungs, calm the nerves, and improve intelligence. *Z. jujuba Mill (ZJM)* and *S. chinensis (SC)* nourish the blood of the heart and liver, calm the nerves and settle the mind, and delay aging. *P. tenuifolia (PT)* and *A. cochinchinensis (AC)* calm the mind, relieve cough, eliminate phlegm, and reduce swelling. *C. yanhusuo (CYHS)* and *C. cassia (CS)* promote blood circulation, remove blood stasis, regulate Qi, and relieve pain. *R. glutinosa (RG)* nourishes the blood and replenishes essence and filling marrow. The combination of these nine TCM components in proper proportions can have the greatest therapeutic effect on "Yu Zheng".

Pharmacological Studies of the Active Compounds of Nine Chinese Medicines Included in JZG

Panax ginseng C.A. Mey

PG is a perennial herb of *Panax* in the family *Acanthopanax* of *Umbelliferae*. Its main producing areas are northeast China, North Korea, South Korea, Japan, and eastern Russia. *PG* contains many effective ingredients, including panaxoside A, B, C, D, E, and F; monosaccharide; *PG* acid (a mixture of palmitic acid, stearic acid, and linoleic acid); vitamins (B1, B2, nicotinic acid, niacinamide, and pantothenic acid); amino acids; choline; enzymes (maltase, invertase, and esterase); spermine; and choleamine.[17,18]

Previous studies have suggested that *PG* has many pharmacological effects, including anticancer,[19] antineuronal apoptosis,[20] antidiabetic,[21] anti-cognitive impairment,[22] antihypertensive,[23] and anti-fatigue[24] activities.

Ginsenoside, an important chemical component of *PG*, has therapeutic effects on colorectal cancer via the SNAIL signaling axis.[25] It could also induce apoptosis and downregulate PD-L1 expression by targeting the NF-κB pathway in lung adenocarcinoma.[26] In addition, ginsenoside has antidepressant effects,[27] prevents cognitive impairment by improving mitochondrial dysfunction in Alzheimer's Disease (AD),[28] ameliorates memory impairments,[29] and has anti-anxiety and anti-stress properties.[30] Previous animal experiments have suggested that stress stimulation can lead to reduced expression of brain-derived neurotrophic factor (BDNF), and they demonstrated that ginsenoside can effectively upregulate BDNF in the hippocampus, downregulate serum cortisol levels, and reduce or reverse changes in the density of synaptic spine neurons in the hippocampus caused by

chronic stress.[31] In addition, abnormal volume and structure of neurons was discovered in the amygdala and hippocampus;[32] ginsenoside could effectively improve these pathological changes.[33] Based on these results, further studies of the specific cellular and molecular mechanisms of ginsenoside's neuroprotective effects as a human antidepressant are warranted.

Ziziphus jujuba Mil

ZJM is a dry and mature seed of *Ziziphus jujuba Mil.var. spinosa (Bunge)*, which is distributed in most parts of China. It nourishes the Heart and liver, calms the Heart and nerves, and promotes the production of body fluid. It is often used for restlessness, palpitations, dreaminess, and sweating.[34] Modern medical research shows that the chemical composition of ZJM is very complex, mainly a variety of zizyphusine, including frangufoline, nuciferine, nornuciferine, norisocorydine, coclaurine, and N-methylbarbine. It contains triterpenoids, including betulinic acid and botulin; flavonoids, including spinosin and zivulgarin;17 kinds of amino acids, including threonine, valine, methionine, leucine, isoleucine, lysine, and phenylalanine; and various metal elements such as potassium, sodium, calcium, zinc, iron, copper, and manganese.[35,36] Some therapeutic functions of *ZJM*, including antioxidant, antihyperglycemic, hepatoprotective, antihyperlipidemic, and sedative activities, have been shown in modern pharmacological studies.[37] Anticancer and anti-inflammation effects have also been observed.[38,39] In addition, by dramatically diminishing the expression of 14-3-3 mRNA levels, *ZJM* could increase tolerance to environmental stresses.[40]

Jujuboside is one of the most effective chemical components of *ZJM* pharmacological function. The pathogenesis of depression is generally believed to be caused by the decreased activity or conduction function of noradrenaline (norepinephrine [NE]) and 5-hydroxytryptamine (5-HT) in the central nervous system.[41] An existing animal model study indicated that Jujuboside exerts an antidepressant effect by reducing the content of 5-HT and dopamine in the prefrontal lobe.[42] According to this analysis, Jujuboside may play an antidepressant role by regulating the 5-HT pathway. However, the exact mechanism remains to be clarified and deserves further study.

Schisandra chinensis (Turcz.) Baill

SC is the dried and mature fruit of *Schisandra chinensis*. Autumn fruits are picked when they are ripe and then dried or steamed to remove stems and impurities.[43] The earliest references to *SC* in TCM appeared in Shennong's Herbal Medicine Classic where it was listed as having the ability to nourish and strengthen the body. It has high medicinal value and is used in combination with Ganoderma to treat insomnia.

The fruit of *SC* contains schisandrin, vitamin C, resin, tannin, and a small amount of sugar. It has astringent effects on lungs and treats cough, nourishes astringent essence, relieves diarrhea, and decreases perspiration. Aromatic oil can be extracted from its leaves. The main function of *SC* is to nourish the lungs and kidneys and remove dampness.[44–46]

The medicinal value of *SC* is mainly reflected in anti-fatigue properties, prevention of mild cognitive impairment,[47,48] enhanced immunity,[49] anticancer effects,[45] amelioration and prevention of Parkinson's disease (PD),[50] amelioration of age-related muscle wasting,[51] and anti-atherosclerotic properties.[52] Schisandrin is the main effective component of *SC*, which was previously considered to be able to treat AD;[53] it has antitumor effects,[54] provides protection against central ischemia recurrence,[55] and treats neurodegenerative disease.[56] In addition, although there is no study of the direct antidepressant effect of schisandrin, it is believed to produce sedative and hypnotic functions by elevating the level of GABA and reducing the level of glutamic acid in the peripheral blood and brain tissues, which has obvious auxiliary effects in the treatment of depression.[57]

Smilax glabra Roxb

SGR is the dry sclerotia of the fungus *Poria Cocos (Schw.) +wolf*. The sclerotia of *SGR* contains many components, including triterpenoids such as pachymic acid, 16α-hydroxyporic acid, methylporic acid, and poric acid; polysaccharides such aspachymaran and high (1, 3), (1,6) branched β-D-glucan H_{11}; and other constituents such as ergosterol, caprylic acid and inorganic elements. *SGR* invigorates the spleen and resolves phlegm, and it also calms the Heart and nerves.[58–60]

Previous studies of *SGR* have shown that it can treat tumors,[61,62] improve depression,[63] relieve hyperglycemia and hyperlipidemia,[64] lessen insomnia,[65] and prevent dementia.[66] It also has potential therapeutic effects for leukemia.[67] *SGR* has sedative and hypnotic effects, and it has obvious therapeutic value for restlessness, palpitations, and insomnia. *SGR* is mainly used in the treatment of depression in compounded preparations. The antidepressant

component of *SGR* and its mechanism require further study. Pachymic acid is one of the main active components of *SGR*, which may raise the expression of glucocorticoid receptor (GR) and recover the negative feedback of hypothalamus-pituitarium-adrenal gland (HPA) axis to relieve depression and illness state.[68]

Polygala tenuifolia Willd

PT is also known as *Yuan Zhi*. It mainly grows in northern, central China, and the Sichuan Province. It calms the mind and improves intelligence, eliminates phlegm, and reduces swelling. It can be used for insomnia, dreaminess, forgetfulness, palpitations, trance, and coughing up phlegm.[69,70] The chemical composition of *PT* is relatively complicated but mainly includes: (1) a variety of saponins that are isolated from the roots of Polygala saponin, and the identified structures are Polygala saponin A, B, E, F, and G (structurally, the basic mother nucleus of Polygala saponin is oleanolic acid, a type of pentacyclic triterpene); (2) oral ketone, which exists only in the form of derivatives in plants (most of the substituents are hydroxyl and methoxy forms, and a few are methylenedioxy); (3) a large number of sugar ester components (its parent core structure has four types [A, B, C, and D], and there are 12 types of substituents); (4) alkaloids, namely R1 R2 N9-formylhalman; and (5) other ingredients, such aspolygalol, 3,4,5-trimethoxycinnamic acid, stigmasterol, a-spinasterol glucoside, and rich fatty oils and resins.[71,72]

Pharmacological research found that *PT* has protective effects on neuronal apoptosis and learning and memory impairment in mice models of AD;[73] improves behavioral abnormalities in mice with depression[74] and improves hippocampal-dependent learning and memory.[75] One of the main active ingredients of *PT* is 3,4,5-trimethoxycinnamic acid (TMCA),[76] which has anticonvulsant,[77] antitumor,[78] antiepileptic,[79] and anti-stress[80] properties and improves cognitive function.[81] The antidepressant mechanism of *PT* includes regulating endocrine functions, protecting cells, increasing the expression of neurotrophic factor BDNF, improving the plasticity of monoamine neurons, and affecting the reuptake process of monoamine neurotransmitters.

Corydalis yanhusuo (Y.H.Chou & Chun C.Hsu) W.T.Wang Ex Z.Y.Su & C.Y.Wu

CYHS is the dried tuber of the *Cordalisambigua Cham.et Schlecht*. It grows under mountain forests or is cultivated in laboratories. *CYHS* activates blood, refreshes Qi, and has analgesic, hypnotic, sedative, and stabilizing properties. A total of more than 20 alkaloids have been identified from the tubers of *CYHS*, including corydaline, dl-tetrahydropalmatine, protopine, L-tetraline, L-tetrahydrocoptisine (L-stylopin), dl-tetrahydroberberine, L-tetrahydrocolumbamine, corybulbine, β-herbadol, β-homoche-lidonine, coptisine, dehydrocorydaline, and corydalmine.[82–85]

CYHS is currently used clinically, mainly for the treatment of drug addiction,[86] as well as for its antiaging, anxiolytic,[87] and antiplatelet aggregation[88] properties and for the treatment of depression.[89] Qi stagnation and blood stasis are primary causes of depression in the theory of TCM. *CYHS* has an obvious effect of promoting Qi and blood circulation. This effect may be the basis of its use in TCM for the treatment of depression. *CYHS* can be used in combination with *Angelica sinensis (Oliv.) Diels* and *Conioselinum anthriscoides* "Chuanxiong" *(syn. Ligusticum chuanxiong)* and could be used in combination with *Campanulaceae* to calm blood and Qi to achieve beneficial effects in the treatment of depression.

One of the main active ingredients of *CYHS*, tetrahydropalmatine, also known as fumarate B (dl-THP),[90] prevents hyperlipidemia,[91] attenuates neuronal apoptosis induced by cerebral ischemia-reperfusion injury,[92] offers neuroprotection,[93] has antitumor effects,[94] provides analgesia,[95] prevents memory impairment,[96] and ameliorates the development of anxiety and depression.[97,98]

Asparagus cochinchinensis (Lour.) Merr

AC is the root of *Asparagus cochinchinensis (Lour.) Merr.* *AC* is long and spindle-shaped, slightly curved, measuring 5 to 18 cm long and 0.5 to 2 cm in diameter. It nourishes yin, reduces heat, and nourishes the lungs and kidneys. *AC* contains aspartin, B-sterol, steroidal saponin, slime, furfural derivatives, and other components. *AC* increases blood cells, enhances the phagocytic function of the reticuloendothelial system, and extends the duration of antibody existence.[99,100]

Progress in the research of *AC* pharmacology has led to the belief that *AC* exhibits a wide range of pharmacological activities, including the treatment of AD[101] and antidepressant, neuroprotective,[102] anti-inflammatory[103] and antitumor [104] effects. Depression can be clinically manifested as insomnia, early waking, memory loss, palpitations, and dizziness. In the TCM theory of Tianwang Buxin Dan, *AC* combined with *PG, Poria*, and *PT* has

a significant effect on treating depression caused by heart, liver, and blood deficiency.

Rehmannia glutinosa (Gaertn.) DC

RG is a perennial herb of the genus *Rehmannia* of the *genus Scrophulariaceae*. Its root is a main component of TCM treatments, and its use was first published in Shennong's Materia Medica. According to the processing method, the medicinal materials are divided into fresh *RG* and dry *RG*. The medicinal properties and efficacies of these three compounds vary greatly. According to the efficacy listed in "Chinese Materia Medica" fresh *RG* is used to reduce heat and cool blood, and *RG* is used to supplement medicine for many TCM. The chemical composition of *RG* is dominated by glycosides, mainly cyclic allene terpenoids, including leonuride, aucubin, catalpol, and rehmannioside A, B, C, and D; sugars, including D-glucose, D-galactose, D-fructose, and sucrose; and a variety of amino acids and inorganic elements.[105–107]

RG has a wide range of clinical applications. It is currently reported that *RG* can be used to treat attention deficit hyperactivity disorder,[108] PD[109], multiple sclerosis,[110] anxiety,[111] and memory disorders,[112] and it inhibits inflammatory responses[113,114] and has anti-fatigue activity.[115] In the theory of TCM, liver depression and blood deficiency are manifested as depression, anxiety, insomnia, palpitations, inattention, and other depressive symptoms. For patients with deficiency of Qi and blood, the effects of Xiao Yao for treating depression can be enhanced by adding *RG*.

Catalpol is one of the main chemical extracts of *RG*. It protects dopaminergic neurons from damage in PD,[116] enhances neurogenesis and inhibits apoptosis of new neurons by activating BDNF,[117] ameliorates hyperactive and impulsive behavior, improves spatial learning and memory,[118] improves axonal growth by regulating miR-124 after ischemia,[119] relieves neuralgia,[120] and has antidepressant effects.[121]

Cinnamomum cassia (L.) J. Presl

CS is in the family of camphor, it is a medium-sized tree of the camphor family, and its bark is gray-brown. The main functions of *CS Presl* include tonifying fire and helping yang, dispersing cold and relieving pain, warming blood vessels, improving yang deficiency, and treating vertigo.[122,123]

The medicinal value of *CS Presl* is mainly reflected in antihypertensive,[124] anti-allergy,[125] antibacterial,[126] and anticancer[127] activities; it is used in the treatment of PD[128] and type 2 diabetes[129] and it improves cognitive dysfunction.[130] In addition, it enhances blood circulation and calms and relieves pain, and it has auxiliary therapeutic effects in depression. Cinnamaldehyde is the main component of *CS Presl*. It improves memory deficits,[131] improves subarachnoid hemorrhage nerve damage and vasospasm,[132] acts as an antidepressant by inhibiting COX-2 in the central nervous system,[133] reduces atherosclerosis,[134] and decreases anxiety-related behavior.[135] The main active compounds of nine Chinese medicines included in JZG and pharmacological mechanisms were summarized in Table 2.

Clinical Application of JZG in the Treatment of Depression

Much evidence has confirmed the efficacy of JZG combined with western medicine in the treatment of depression. In our review, we performed a systematic review of clinical trial articles on PubMed, Embase, Cochrane, Web of Science, Wanfang (http://www.wanfangdata.com.cn/index.html), Weipu (http://www.cqvip.com/) and CNKI (https://www.cnki.net/) database during 1984–2019 (Table 3). JZG was added to duloxetine for the treatment of patients with depression and compared with duloxetine treatment alone: Wang et al found that the scores on the Hamilton Depression Scale (HAM-D) and self-ratings of depression in the combination group were significantly improved, and the levels of 5-hydroxytryptamine and cortisol in the combination treatment group were also significantly higher than those in the single-drug treatment group. Hu et al enrolled 126 patients with depression and randomly divided these patients into two groups: 62 patients were treated with bupropion combined with JZG and 64 patients were treated with bupropion alone. The HAM-D scores of the two groups were compared at weeks 2, 4, 6, and 8 of treatment, and the researchers found that the patients in the combination treatment group achieved better results than those treated with bupropion alone. Additionally, the longer the duration of JZG combination treatment, the more obvious the therapeutic effects these patients achieved. The combination of JZG and classical Western antidepressants could improve the efficacy of Western medicine alone, suggesting that JZG has a good synergistic effect with Western medicine.

Previous studies also compared the therapeutic effects of JZG with those of western medicine. Li et al compared

Table 2 Main Active Compounds of Nine Chinese Medicines Included in JZG and Pharmacological Mechanisms

TCM Name	Main Effective Ingredients and Pharmacological Mechanisms	References
Panax ginseng C.A. Mey	Ginsenoside • Induce apoptosis and downregulate PD-L1 expression by targeting the NF-κB pathway ○ Improving mitochondrial dysfunction • Upregulate BDNF in the hippocampus, downregulate serum cortisol levels	22, 24, 31
Ziziphus jujuba Mil	Jujuboside • Exerts an antidepressant effect by reducing the content of 5-HT and dopamine in the prefrontal lobe	27
Schisandra chinensis (Turcz.) Baill	Schisandrin • Elevate the level of GABA and reduce the level of glutamic acid in brain tissues	46
Smilax glabra Roxb	Pachymic acid • Raise the expression of GR and recover the negative feedback of HPA axis to relieve depression	68
Polygala tenuifolia Willd	3,4,5-trimethoxycinnamic acid • Regulate endocrine functions, increase the expression of neurotrophic factor BDNF, improve the plasticity of monoamine neurons, and affect the reuptake process of monoamine neurotransmitters	76, 77, 80
Corydalis yanhusuo W.T.Wang ex Z.Y.Su & C.Y.Wu	Tetrahydropalmatine • Attenuates neuronal apoptosis induced by cerebral ischemia-reperfusion injury	91
Asparagus cochinchinensis (Lour.) Merr	Aspartin • Increase blood cells, enhance the phagocytic function of the reticuloendothelial system, and extend the duration of antibody existence	99, 100
Rehmannia glutinosa (Gaertn.) DC.	Catalpol • Protect dopaminergic neurons from damage • Enhance neurogenesis and inhibit apoptosis of new neurons by activating BDNF • Improve axonal growth by regulating miR-124	116, 117, 119
Cinnamomum cassia (L.) J. Presl	Cinnamaldehyde • Inhibit COX-2 in the central nervous system	133

Abbreviations: TCM, Traditional Chinese Medicine; BDNF, brain-derived neurotrophic factor; GABA, γ-aminobutyric acid; GR, glucocorticoid receptor; HPA, hypothalamus-pituitarium-adrenal gland.

the therapeutic effects of JZG and fluoxetine in patients with depression. The study found that after 8 weeks of treatment, the HAM-D scores of the two groups were significantly improved. The therapeutic effect of JZG was similar to that of fluoxetine, which confirmed the therapeutic effect of JZG on depression. However, the incidence of adverse reactions in the JZG treatment group was 9%, which was far lower than that of the fluoxetine group (47.7%). At present, there are few comparative studies on the effectiveness of JZG and classic antidepressants. The conclusion of this study requires more samples and multi-center clinical studies for further verification.

Moreover, JZG is widely used in diseases associated with depression. At present, the most studied of these related conditions is postpartum depression. Lin et al have achieved good results in the treatment of postpartum depression with a combination of sertraline and JZG, and, because of the decreased sertraline dosage required when used in combination with JZG, the rate of adverse reactions was significantly reduced. Wang et al achieved a similar conclusion: JZG combined with sertraline hydrochloride has a significant effect on the treatment of postpartum depression. The improvement in sex hormone levels (estradiol and progesterone) in patients receiving combined treatment with JZG was better than that in patients treated with sertraline hydrochloride alone. However, the safety of JZG for postpartum depression needs to be further evaluated, such as the concentration of the drug in breast milk and its possible effect on infants.

Table 3 Characteristics and Findings in Clinical Studies Reviewed

Authors, Years	Study Type	Country Location	Study Group	Therapeutic Intervention		Treatment Course	Main Efficacy Evaluation Index	Key Findings
				Treatment Group	Control Group			
Liu et al, 2015	Prospective Cohort	China	40 P, 40 C	JZG + Fluoxetine	Fluoxetine	6 weeks	TER, ADR, HAMD	Fluoxetine combined with JZG could effectively improve depression symptoms in elderly patients with depression
Hu et al, 2012	Prospective Cohort	China	62 P, 64 C	JZG + Bupropion	Bupropion	8 weeks	TER, ADR, HAMD	JZG could improve the antidepressant effect of bupropion
Hu et al, 2014	Prospective Cohort	China	58 P, 60 C	JZG + Fluoxetine	Fluoxetine	8 weeks	TER, ADR, HAMD	JZG improves depression in patients with anxiety, and could be used as a synergist for fluoxetine
Zheng et al, 2011	Prospective Cohort	China	58 P, 60 C	JZG + Escitalopram	Escitalopram	8 weeks	TER, ADR, HAMD	JZG improves anxiety symptoms caused by escitalopram in the early stage of treatment
Han et al, 2007	Prospective Cohort	China	30 P, 30 C	JZG + Escitalopram	Escitalopram	12 weeks	TER, ADR, HAMD	JZG improves post-stroke depression symptoms
Wang et al, 2014	Prospective Cohort	China	66 P, 65 C	JZG + Duloxetine	Duloxetine	6 weeks	TER, ADR, HAMD	JZG has a synergistic effect in enhancing the clinical treatment of depression
Xue et al, 2017	Prospective Cohort	China	44 P, 44 C	JZG + Fluvoxamine	Fluvoxamine	8 weeks	TER, ADR, HAMD	JZG has good clinical effect in treating senile depression
Wang et al, 2012	Prospective Cohort	China	44 P, 43 C	JZG + Sertraline	Sertraline	8 weeks	TER, ADR, HAMD	JZG has obvious therapeutic effect on postpartum depression
Lin et al, 2017	Prospective Cohort	China	50 P, 50 C	JZG + Sertraline	Sertraline	6 weeks	TER, ADR, HAMD	JZG has obvious therapeutic effect on postpartum depression
Wang et al, 2011	Prospective Cohort	China	33 P, 33 C	JZG	Paroxetine	6 weeks	TER, ADR, SDS	JZG could be used to treat depression symptoms in diabetic patients
Li et al, 2011	Prospective Cohort	China	44 P, 44 C	JZG	Fluoxetine	8 weeks	TER, HAMD	JZG is more effective than fluoxetine in treating depression
Wang et al, 2012	Prospective Cohort	China	61 P, 60 C	JZG + Venlafaxine	Venlafaxine	8 weeks	TER, ADR, HAMD	JZG combined with Venlafaxine has a significant effect on perimenopausal depression

(*Continued*)

Table 3 (Continued).

Authors, Years	Study Type	Country Location	Study Group	Therapeutic Intervention		Treatment Course	Main Efficacy Evaluation Index	Key Findings
				Treatment Group	Control Group			
Guo et al, 2016	Prospective Cohort	China	40 P, 40 C	JZG + Sertraline	Sertraline	6 weeks	TER, ADR, HAMD	JZG combined with sertraline has significant effect on post-stroke depression

Abbreviations: ADR, adverse drug reactions; HAMD, Hamilton Depression Scale; TER, total effective rate; SDS, self-rating depression scale; P, patients; C, controls.

Taken together, these clinical studies have shown that JZG is effective in treating depression and has fewer side effects than conventional drugs. However, current research of JZG in the treatment of depression is mostly limited to Chinese patients, and the number of patients with depression included in the studies is small. In the future, large-scale randomized controlled studies will be needed to further confirm the efficacy of JZG in depression.

The Pharmacological Mechanism of JZG in the Treatment of Depression

There is currently a lack of research regarding the mechanism of JZG in the treatment of depression. However, through the study of the effective molecular structures of the nine components of JZG, it is not difficult to determine that the effective molecules in JZG play active roles in the treatment of depression through various pathways. Ginsenoside can lessen unpredictable mild stress and depression-like effects by regulating the NF-κ B/NLRP3 pathway in a rat model;[136] ginsenoside may also protect depression-like behavior by inhibiting glial activation, synaptic damage, and neuronal apoptosis.[137] Schisandrin protects depression-like behaviors caused by chronic unpredictable mild stress through GDNF/ERK1/2/ROS and PI3K/AKT/NOX signaling pathways.[138] Tetrahydropalmatine is associated with anxiolytic- and antidepressant-like profiles in the elevated plus maze (EPM) test, probably by modifying the expression of neuropeptide Y (NPY) and corticotrophin-releasing factor (CRF) in the hypothalamus.[98] Catalpol significantly protects against depression and neurodegeneration by elevating serotonin and BDNF levels; catalpol could increase mitochondrial biogenesis and activation of the PI3K/Akt pathway for insulin sensitization.[139] Cinnamaldehyde shows antidepressant effects, possibly by acting on the endocannabinoid system, in the forced swim test.[133]

In addition to JZG, there are also classic formulations of TCM that have obvious effects in the treatment of "Yu Zheng". Xiao Yao San (XYS) contains gardenia and paeonol; it soothes the liver and spleen, promotes Qi, and decreases stagnation. Some researchers have summarized the antidepressant mechanism of XYS in terms of neurotransmitters, neurotrophins, hypothalamic-pituitary-adrenal axis, amino acids, lipid and energy metabolism, and inflammatory factors, showing that XYS has multiple targets for producing antidepressant effects by regulating metabolic balance in the body.[68,140–142] Chaihu Shugan San has a significant effect on the treatment of liver Qi stagnation syndrome, which can significantly reduce the degree of "Yu Zheng" in patients. Studies have shown that Chaihu Shugan San can better improve brainstem auditory and visual evoked potentials in patients with primary depression, reduce abnormal potential signals in the cerebral cortex, regulate the release of neurotransmitters such as serotonin, increase serum zinc levels in patients with depression, and improve patients' cognitive function, thus achieving relief of patients' depression symptoms. Animal experiments show that Chaihu Shugan San can lessen clinical symptoms and has an obvious therapeutic effect on depression in rats.[143–146] Xiao Chaihu decoction comes from the "Treatise on Febrile Diseases" and acts to reconcile Shaoyang and regulate the stomach; it is often used to treat liver stagnation and poor vitality. Xiao Chai Hu decoction can promote the recovery of BDNF levels, improve levels of neurofunctional factors, and enhance sleep quality.[147,148] Other formulas, such as Baihe Dihuang decoction, can significantly increase the content of dopamine and serotonin in the cerebral cortex, hypothalamus, hippocampus, and striatum of rats;[149] Guipi decoction increases the levels of serotonin, NE, and dopamine in the hippocampus;[150] and Xuefu Zhuyu decoction can significantly increase serotonin concentration and promote

the expression of serotonin-1A receptors.[151] These formulas also have ideal therapeutic antidepressant effects.

In recent years, it has been found that ketamine has the advantages of fast onset and long duration of efficacy, and it is effective for the treatment of refractory depression.[152] Ketamine, as an N-methyl-D-aspartic acid (NMDA) receptor antagonist, has a different mechanism from traditional5-HT reuptake inhibitors, which provides a new target for the development of novel antidepressants.[153] Ketamine may play an antidepressant role through a variety of mechanisms, including (1) blocking the effect of glutamate on NMDA receptors; (2) blocking NMDA receptors and activating α-amino -3-hydroxy-5-methyl-4-isoxazolpropionic acid receptor (AMPAR);[154] (3) reducing the inhibition of the presynaptic glutamatergic pathway by inhibiting the activity of GABA's effect, leading to increased glutamate release in the presynaptic membrane;[155] and (4) upregulating the expression level of BDNF.[156] By studying the mechanism of ketamine, it is not difficult to observe that some components of JZG have similar antidepressant mechanisms as ketamine. For example, *CS Presl* improves neuroinflammation-mediated NMDA receptor dysfunction and memory deficits by blocking the NF-kappa B pathway in presenilin1/2 conditional double knockout mice;[131] *PT* produces antiseizure effects by modulating GABAergic systems in mice[79] and increasing the expression of neurotrophic factor BDNF; and *Schisandrin* could elevate the level of GABA and reduce the level of glutamic acid in brain tissues, which has obvious auxiliary effects in the treatment of depression.[57] These similarities may yield more clues for investigations of the pharmacological mechanisms of JZG in the treatment of depression.

Active Biomarkers of JZG in the Treatment of Depression

TCM, which has thousands of years of clinical application history, plays an extremely important role in the process of human disease prevention and treatment. The modernization of TCM is an inevitable process of scientific development. Although previous studies have extensively explored the material basis and mechanisms of the role of TCM and have accumulated a wealth of experience and data, how TCM actually works is still unclear and its clarification is an ongoing part of the modernization of this ancient practice.

The clinical application of TCM is mainly based on prescriptions (compounds), which can achieve the effect of disease prevention and treatment through the reasonable compatibility of various herbs. However, in this complex material system, how does each medicine play a role in treating diseases? In recent years, studies have shown that the efficacy of TCM is the result of multi-component and multi-target interactions. In fact, this kind of understanding is only the expression of the surface phenomenon of the action of TCM and cannot reflect the laws and mechanisms of the actions of TCM. The basis of the function of TCM should be the reasonable and organic combination of various effective ingredients. Its mode is to act on multiple targets related to diseases in the body in various ways and to play a role in the overall regulation of the body.

To further elucidate the JZG anti-depression targeting mechanism, we construct a pharmacological network and the mechanism of action of JZG against depression was studied by integrating pharmacological concepts (Figure 1).

According to the parameters of absorption, distribution, metabolism and excretion, we first screened the active ingredients of JZG by searching the pharmacological database of the traditional Chinese medicine system platforms (TCMSP) (http://www.tcmspw.com/). A total of eight active biomarkers in JZG were identified, including ginsenoside, jujuboside, schisandrin, pachymic acid, 3,4,5-trimethoxycinnamic acid, tetrahydropalmatine, catalpol, and cinnamaldehyde. 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 2).

The Swiss Target Prediction database (http://www.swisstargetprediction.ch/) is a web server for target prediction of bioactive small molecules. The targets of active biomarkers in JZG were screened in this database. The Online Mendelian Inheritance in Man (OMIM) database, a compendium of human Mendelian inheritance, is a database of human genes and genetic disorders. It mainly focuses on genetic diseases and includes text information and related reference information, sequence records, maps, and other related databases. In this study, the targets of depression were obtained from the OMIM database (http://omim.org/).

To elaborate on the multicomponent treatment system that JZG exerts in the treatment of depression, a comprehensive interaction network was applied to identify the common genes of active components in JZG and depression; in

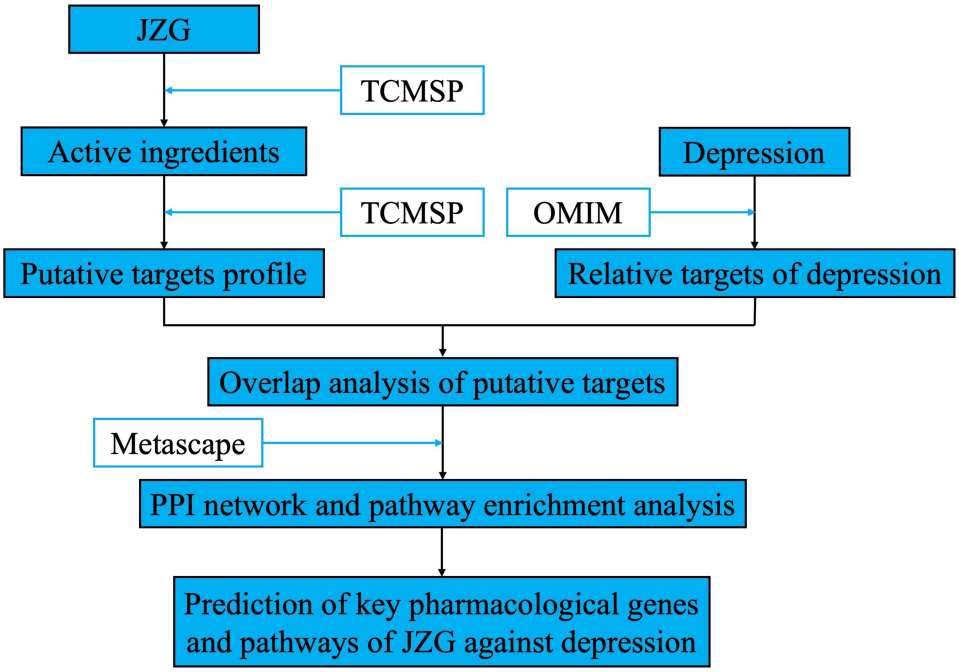

Figure 1 The technical strategy of this research based on network pharmacology for deciphering key pharmacological genes and pathways of JZG against depression.
Abbreviation: JZG, Jiuwei Zhenxin granules.

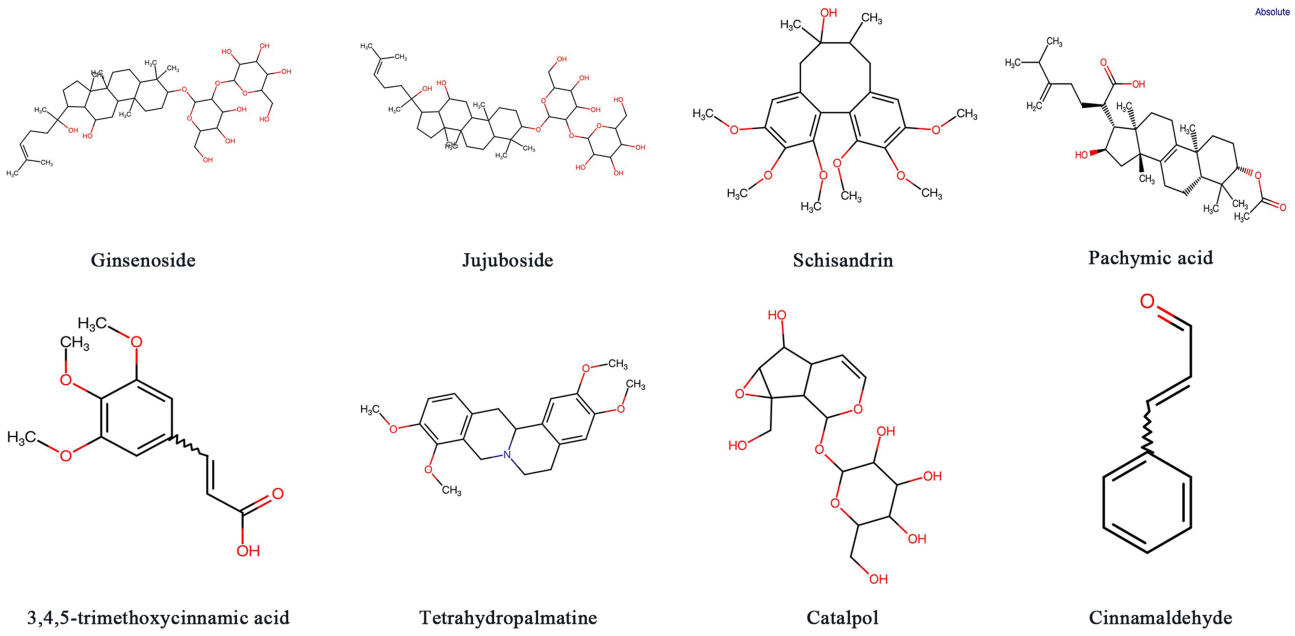

Figure 2 The 2-D structures of effective biomarkers in JZG. JZG, Jiuwei Zhenxin granules.
Abbreviation: JZG, Jiuwei Zhenxin granules.

addition, a Gene Ontology (GO) analysis was performed to standardize description of the common genes. These methods are used to better construct and reveal the relationship between active ingredients in JZG and depression target genes.

A total of 854 target genes of JZG and 874 target genes of depression were obtained; as a result, 21 targets of both JZG and depression were identified (Figure 3). Cytoscape is an open-source software platform for visualizing complex networks. We used Cytoscape to construct the

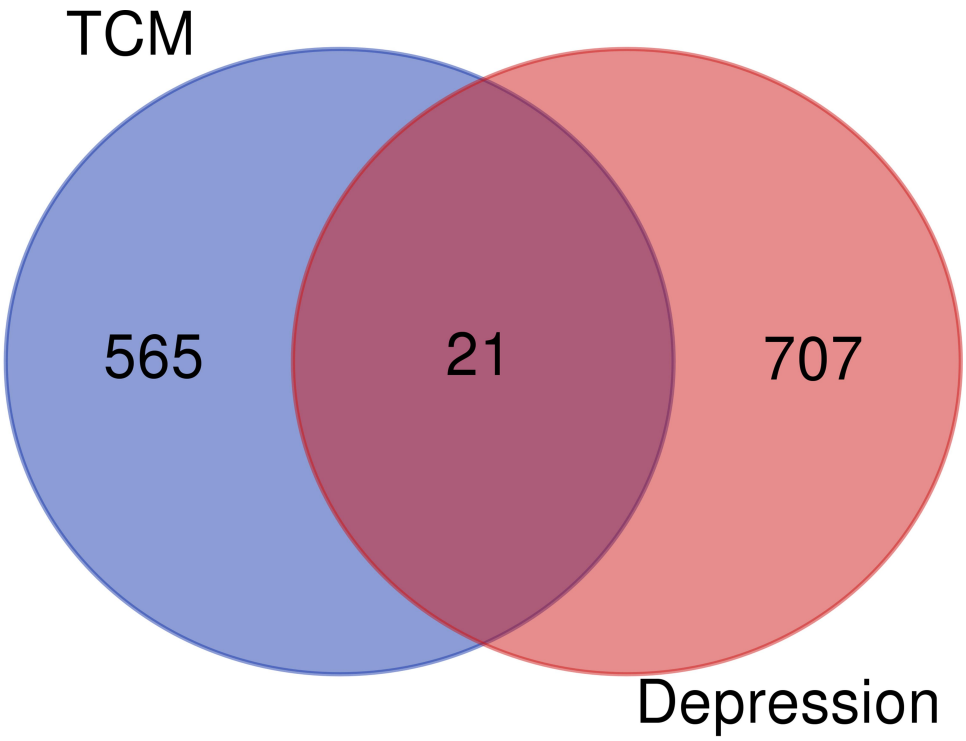

Figure 3 A total of 21 targets of both JZG and depression were identified.
Abbreviations: JZG, Jiuwei Zhenxin granules; TCM, traditional Chinese medicine.

protein-protein network consisting of 21 nodes (Figure 4). The top 12 GO-enriched terms are listed in Table 4 and visualized in Figure 5, which was constructed using the Metascape (http://metascape.org) database.

Conclusion and Prospects

TCM may have a unique position to play in the treatment of depression: it not only has shown promise in lessening clinical symptoms, but it is also well tolerated and is associated with good compliance among patients. TCM compounds have characteristics of multi-component, multi-target, and dialectical treatments. It has the possibility be used in combination with western medicine to treat depression and this may help to reduce the occurrence of adverse reactions. Moreover, it may produce a synergistic effect, potentially enhancing the efficacy of western medicine. These are areas all in need of further research.

In recent years, much laboratory and clinical research have been conducted to reveal the treasure trove that is TCM, and many antidepressant TCMs with therapeutic effects have been identified. Still, there are problems related to TCM that need to be solved. First, there is still no unified standard for syndrome differentiation or treatment principles of depression in TCM. Doctors often rely only on clinical experience to differentiate and treat syndromes, which is also the problem with the modern DSM classification of mental illnesses. In fact, the diagnostic validity and stability of major psychiatric diagnoses is an area of perennial debate and controversy. It is known that the differential or provisional diagnosis may be rather imprecise and depends largely on a subjective assessment of the patient's cross-sectional mental state at the specific time point [157]. Second, the antidepressant effects of TCM are evaluated clinically using HAM-D (decreased scores) and psychiatric symptoms (disappeared or improved), but there are no objective standards to evaluate the therapeutic effects. Third, there is a lack of in-depth systematic research on the antidepressant effects of TCM. Some more specific mechanistic studies, such as "omics" technologies might provide greater information on the metabolite changes and possible pharmacological mechanisms of JZG.[158]

JZG is a type of TCM. According to TCM theory, it nourishes the heart and spleen, tonifies Qi, and tranquilizes the spirit, and it has certain auxiliary therapeutic effects in depression. Research on the components of Chinese herbal medicines have found that the effective compounds of JZG play a role in the pharmacological basis of modern medicine.

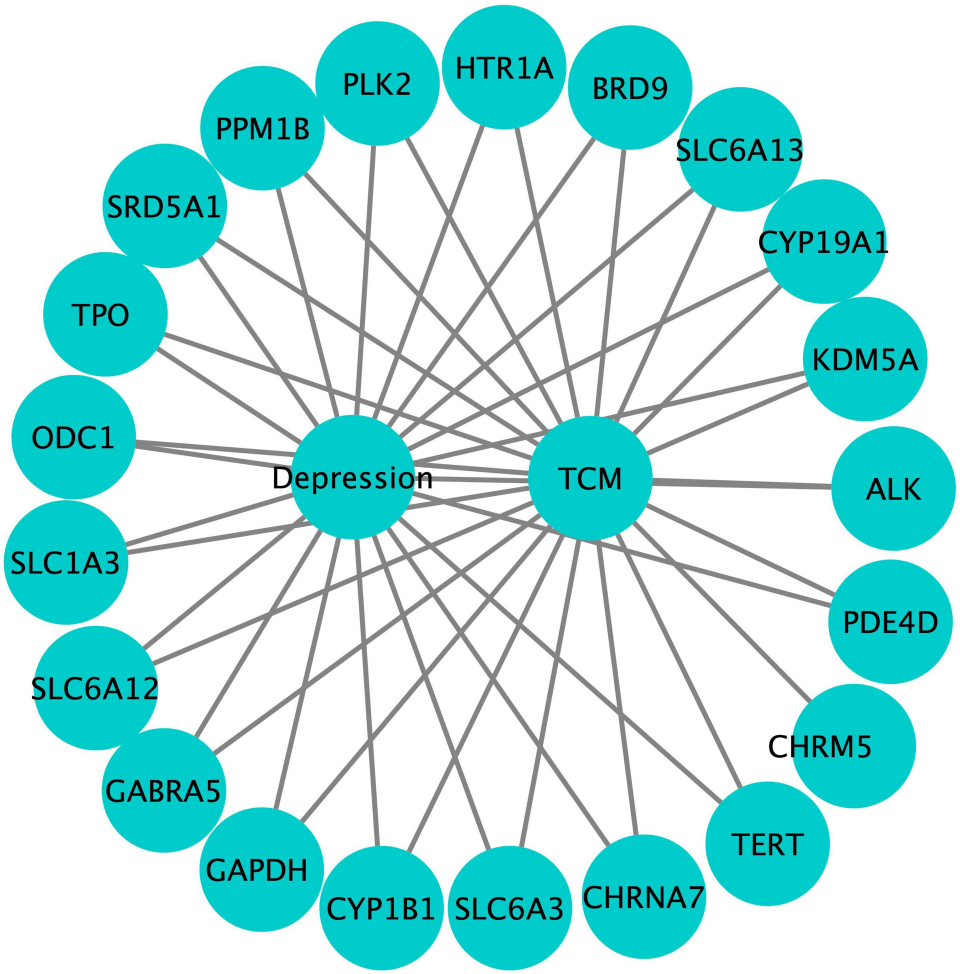

Figure 4 A total of 21 targets were used to establish the regulation network in Cytoscape.
Abbreviation: JZG, Jiuwei Zhenxin granules.

In clinical practice, the results of current clinical controlled studies show that the combination of JZG and antidepressants in classic modern drugs can improve patients' depressive symptoms better and faster than simple classic modern drugs, and can extend the effective period of drugs. However, this conclusion needs further confirmation by high

Table 4 Top 12 Clusters with Their Representative Enriched Terms of JZG on the Depression

GO	Category	Description	Count	%	Log10 (P)
GO: 0007610	GO Biological Processes	Behavior	8	38.1	−7.7
R-HSA-112315	Reactome Gene Sets	Transmission across Chemical Synapses	6	28.57	−7.04
GO: 0042133	GO Biological Processes	Neurotransmitter metabolic process	5	23.81	−6.75
GO: 1,901,615	GO Biological Processes	Organic hydroxy compound metabolic process	6	28.57	−5.33
GO: 0045766	GO Biological Processes	Positive regulation of angiogenesis	4	19.05	−4.58
GO: 0097164	GO Biological Processes	Ammonium ion metabolic process	4	19.05	−4.55
M 66	Canonical Pathways	PID MYC ACTIV PATHWAY	3	14.29	−4.37
GO: 0007568	GO Biological Processes	Aging	4	19.05	−3.81
GO: 0035690	GO Biological Processes	Cellular response to drug	4	19.05	−3.58
GO: 0001817	GO Biological Processes	Regulation of cytokine production	5	23.81	−3.5
R-HSA-71291	Reactome Gene Sets	Metabolism of amino acids and derivatives	3	14.29	−2.41
GO: 0051090	GO Biological Processes	Regulation of DNA-binding transcription factor activity	3	14.29	−2.23

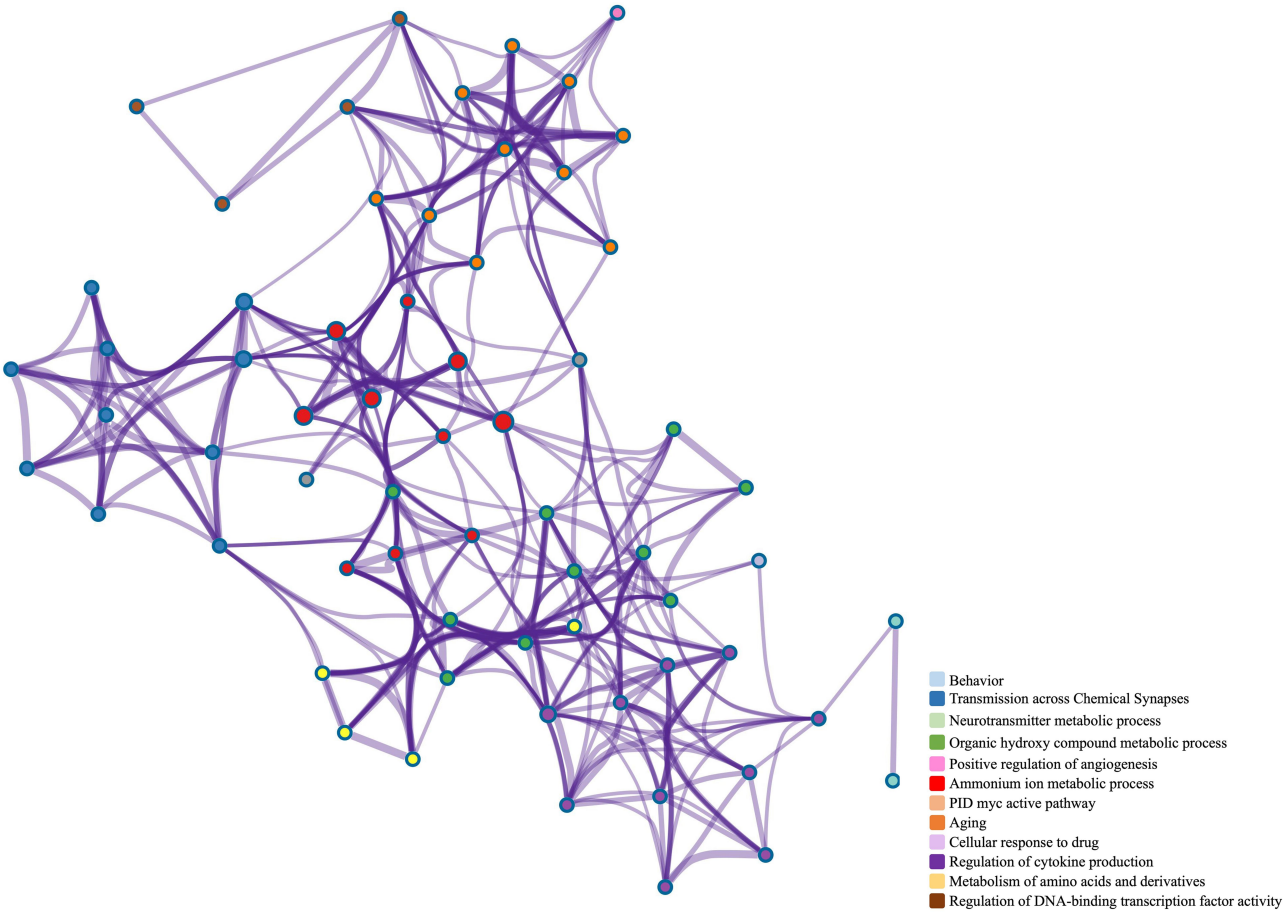

Figure 5 Network of enriched terms. (Size of the circle relates to *p*-value; terms containing more genes tended to have a more significant *p*-value.).

quality double blinded placebo controlled randomized clinical trial. In order to further clarify the pharmacological mechanism of JZG, we predicted the possible mechanism of JZG in the treatment of depression for the first time by means of bioinformatics analysis, which can be used to accelerate studies on the mechanism of JZG in depression and will further promote the modernization of TCM.

Author Contributions

J.W. contributed to the literature search, data extraction, and data analysis. J.W. and X.W. contributed to the project design and writing of the manuscript. All authors have read and approved the final version of the manuscript. 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; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests for this work.

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