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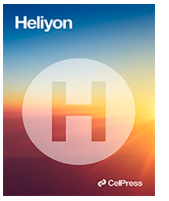

Review article

Progress of research on the treatment of depression by traditional Chinese medicine prescriptions

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ABSTRACT

Depression is a common psychiatric disorder that belongs to the category of "Depression Syndrome" in traditional Chinese medicine (TCM), and its etiology and pathogenesis are complex and unclear. It is characterized by high prevalence, high disability rate, and high recurrence rate, which seriously affect human health, and its treatment has become a research hotspot worldwide. At present, the antidepressants commonly used in the clinic are mainly Western medicine (WM), but there are problems such as frequent side effects and poor efficacy. Studies have found that the use of TCM prescriptions in the treatment of depression can achieve the same effect as WM; and when TCM prescriptions are combined with WM, the efficacy can be enhanced while the adverse effects of WM can be reduced. Pharmacological studies related to the treatment of depression with traditional Chinese medicine prescriptions (TCMPs) have focused on the neurobiochemical system, gut microbes, and energy metabolism in mitochondria. No one has yet reviewed the pharmacological mechanism of TCMPs for depression. So, this paper reviews the pharmacological mechanism of TCMPs for depression from the perspective of TCMPs, introduces the progress of research on classical TCMPs for depression and their antidepressant mechanism. This article aims to promote the application of TCMPs in the clinic and provide a new therapeutic idea for the clinical treatment of depression.

1. Introduction

Depression is a prevalent psychiatric disorder characterized by persistent low mood or lack of happiness. Its incidence continues to rise due to the increasing pressures of life. It is a lifelong illness characterized by recurrent episodes, and women are significantly more likely to be affected than men [1]. It can have a serious impact on individuals' daily routines, including their studies, work, and personal lives. In some cases, patients may even harm themselves or contemplate suicide [2,3]. The World Health Organization predicts that by 2030, cases of depression will surpass those of all types of cardiovascular disease combined. Additionally, the most

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Table 1
Composition and efficacy and action of tradition Chinese medicine prescription.

Names of Classic traditional Chinese medicine prescriptions	Corresponding types of syndromes	Composition and volume	Efficacy and Action	Monomers and references
Yueju Wan	Depressions of the liver and spleen	Nutgrass Galingale Rhizome, Szechuan Lovage Rhizome, Rhizome of Swordlike Atractylodes, Medicated Leaven, Cape Jasmine Fruit, each 10g.	The index of ethology of CUMS mouse was improved; 5-HT↓; Plasma CORT↑ [17]	Gardenia yellow pigment (GYP) [18]
Suanzaoren Decoction	Liver Blood Deficiency	Spina date seed (Fried) 15g; Liquorice Root 3g; Common Anemarrhena Rhizome, PORIA, Szechuan Lovage Rhizome, each 6g.	Increasing sucrose consumption; BDNF↑; TrKB↑ [19]	Spinosin and 6‴-feruloylspinosin [20]
Xiaoyao San	Depression of the liver leads to Fire	Liquorice Root (Roasted lightly) 15g; Chinese Angelica Root, PORIA, White Peony Root, Largehead Atractylodes Rhizome, Root of Chinese Thorowax, each 30g	Enhancing the depressive-like behavior; CORT, UCN2↓; BDNF, TrKB, mTOR↑ [21]	Coumarins angelicin [22]; Xanthoangelol and 4-Hydroxy-derricin [23]; Atractylenolide III [24]
Pinellia and Magnolia Decoction	Phlegm-Qi stagnation	Pinellia Tuber 12g, Mangnolia officinalis 9g, PORIA 12g, Fresh Ginger 15g , Perilla Leaf 6g.	Increasing sucrose consumption; HDLC↑; TG, SOD, NOS, MDA↓ [25]	Magnolia bark (PMB), Poria (PPO) [26].
Guipi Decoction	Heart and Spleen Deficiency	Largehead Atractylodes Rhizome, Poria with hostwood, Radix Astragali, Dried Longan Prlp, Spina date seed (Fried, shell removal), Each 18g; Ginseng, Costus Root, Each 9g; Liquorice Root 6g; Chinese Angelica Root 3g; Thinleaf Milkwort Root-bark 3g	BDNF level in the hippocampus CA3 area of CUMS rats↑; Increasing sucrose consumption [27]	Astragaloside IV (AS-IV) [28]
GanMai Dazao Decoction	Deficient Cultivation of Heart-spirit	Liquorice Root 9g, Wheat 15g, Chinese Date 10 dates.	DOPAC and DOPAC/DA ratio↓, 5-HT and DA↑ [29]	Licorice total flavonoids, Liquiritin [30]
Chaihu Shugan Powder	Liver Depression and Qi Stagnation	Root of Chinese Thorowax 12g; Rhizome of Swordlike Atractylodes, Nutgrass Galingale Rhizome, Szechuan Lovage Rhizome, Cape Jasmine Fruit, Medicated Leaven, each 9g.	Increasing sucrose consumption, reduce depressive behaviors; miR-124↓; MAPK14 and Gria3 mRNA↑ [31]	Saikosaponin A [32]; Ginsenoside Rb (1) [33]
Yinao Jieyu Fang	Kidney deficiency and liver depression	Manyprickle Acanthopanax sp. root 30g, Radix curcumae 10g, Fructus Schisandrae chinensis 15g, FructusGardeniae sp. 10g, Salviae miltiorrhizae 15g, and Rhizoma Chuanxiong 15g.	Alleviating depressive behavior; Decrease the immobility time; Increase sucrose consumption.Notch 1 mRNA↑ [34]	Curcumin [35]
Baihe Shugan Anshen Docoction	Deficient Cultivation of Heart-spirit	Lily Bulb 12g, Root of Chinese Thorowax 9g, Spina date seed 10g, Hypericum Perforatum 3g, Turmeric 9g, Ginseng 6g, Purple perilla 6g.	Enhancing the depressive-like behavior; CORT, ACTH, CRH↑ [36]	Sulfated Pachymaran [37]
Sijunzi Decoction	Qi Deficiency and Phlegm Stasis	Ginseng, Largehead Atractylodes Rhizome, PORIA, each 9g; Liquorice Root 6g.	Reducing the immobility time in the mouse tail suspension and forced swimming tests; BDNF, PACAP↑ [38]	Nonpolysaccharide NPS, Active polysaccharide S-3 [39]
Xingpi Jieyu Fang	Liver Depression and Spleen Deficiency	American Ginseng, Acorus gramineus, Turmeric Root-tuber, Hypericum Perforatum.	Alleviating depressive behavior; Repress astrocyte activation in depression rats; Elevate 2-DG uptake, ATP, glucose-1-phosphate, BDNF↓ [40]	Ginsenoside Rg1 [41]
Baihe Dihuang Decoction	Yin deficiency in both the heart and lungs	Lily Bulb 24g, Drying Rehmannia Root Juice 200 ml.	lncRNA Neat1 and Malat1↑; miRNA-144-3p and miRNA-15b-5p↓; Gad-67, VGAT, GAT-3↑ [42]	Verbascoside [43]

Notes: CUMS:Chronic unpredictable mild stress; 5-HT: 5-hydroxytryptamine; BDNF: Brain-derived neurotrophic factor; TrKB: Tropomyosin receptor kinase B; CORT: Corticosterone; UCN2: Urocortin 2; mTOR: Mammalian target of rapamycin; HDLC: High density lipoprotein cholesterol; TG: Triglyceride; SOD: Superoxide dismutase; NOS: Nitric oxide synthase; MDA: Malondialdehyde; DOPAC: 3-dihydroxyphenylacetic acid; DA: Dopamine; miR-124: MicroRNA-124; MAPK14: Mammalian Arylalanine Proteins 14; Gria3: Glutamate Ionotropic Receptor AMPA Type Subunit 3; Notch 1: Neurogenic locus notch homolog protein 1; ACTH: Adrenocor ticotropic hormore; CRH: Corticotropin releasing hormone; PACAP: Pituitary Adenylate Cyclase Activating Polypeptide; 2-DG: 2-Deoxy-D-glucose; lncRNA: Long non-coding RNA; Neat1: Nuclear paraspeckle assembly transcript 1; Malat1: Metastasis associated in lung denocarcinoma transcript 1; Gad-67: Glutamate Decarboxylase 67; VGAT: Vesicular GABA transporter; GAT-3: GABA transporter type 3; ATP: Adenosine Triphosphate.

recent Global Burden of Disease study found that depression accounted for 1.85 % of all disability-adjusted life years (DALYs) worldwide [4]. The China Mental Health Survey (CMHS) project conducted a study between 2012 and 2015, examining the epidemiology of mental disorders and the use of mental health services across the country. The results indicated that the lifetime prevalence of depression was 8.0 % for women and 5.7 % for men [5].

Depression is a complex condition with multifactorial pathogenesis and etiology, involving physiological changes in the body and environmental factors. It can occur alone or in conjunction with other diseases, and effective treatments are not yet established. There are several hypotheses regarding the pathogenesis of depression, including abnormal expression of neurotransmitters and their receptors, plasticity of hippocampal neurons, changes in related cellular pathways, disorders in the regulation of the hypothalamic-pituitary-adrenal axis (HPA axis). In addition, the secretion of inflammatory factors and oxidative stress, the dysregulation of intestinal microorganisms, and the disorders of energy metabolism in mitochondria are also believed to be closely related to the onset of depression [6,7].

Although a variety of antidepressant medications are currently used clinically for the treatment of depression, most western medicines (WM) are the accompanied by a variety of adverse effects. Common adverse effects of WM include withdrawal reactions, weight gain [8], emotional numbness, sleep-related dyskinesia, tremor, and abnormal bleeding [9]. Currently, selective serotonin reuptake inhibitors and monoamine oxidase A inhibitors, developed to address the imbalance of monoamine transmitters, are widely used in clinical settings. However, long-term administration of these drugs can reduce receptor sensitivity, leading to a delay in clinical efficacy. Additionally, this class of drugs has a low efficacy rate, greater side effects, limited options, and is prone to duplication. These shortcomings must be addressed [10].

While traditional single-target antidepressant drug therapy may not be ideal, traditional Chinese medicine (TCM) has a long history of use in the treatment of depression [11]. TCM has unique insights into depression, and its treatment system is relatively comprehensive. And TCM therapy can help alleviate adverse reactions caused by long-term WM treatment. During the treatment, rehabilitation, and conditioning of depression, TCM's multi-target, multi-pathway, multi-level, and multi-mechanism mode of action can provide certain advantages [12]. However, this also makes it difficult to study its concretization.

There has not been any review on the antidepressant effects of traditional Chinese medicine prescriptions (TCMPs). So, this paper summarizes the pharmacological mechanisms in the treatment of depression with TCMPs, from the perspective of TCMPs for the treatment of depression, as well as the related research progress by conducting relevant literature searches in databases such as PubMed, CNKI, and Web of Science. TCMPs can be used to treat depression by regulating the expression level of neurotransmitters and their receptors, regulating neuronal plasticity and related pathways, inhibiting the secretion of inflammatory factors, regulating the HPA axis, improving the gastrointestinal flora, and regulating mitochondrial energy metabolism. This article aims to provide a certain reference basis for the scientific research of TCMPs and promote the application of TCMPs for the treatment of depression in clinical practice.

2. Pharmacological mechanism of TCMPs for the treatment of depression

Summarizing discussions on depression, it is generally believed that the onset of depression is closely related to emotional and psychological distress. Professor Ding suggests that patients with depression may experience a series of symptoms, such as lethargy, apathy, worry, and anxiety, due to "stagnation of Yang Qi and mental decadence" [13]. Other medical practitioners believe that depression can be caused by imbalances in the five internal organs. Treatment should focus on promoting the interpromotion and restraint of the five elements of heart, liver, spleen, lungs and kidneys. And it is important to avoid basing treatment solely on one aspect of the condition [14]. Another scholar has suggested that there is a close physio-pathological relationship between the brain, heart, and tri-jiao. The recommended treatment is to warm-benefiting the brain and heart, unclog the tri-jiao, and digest and regulate the Qi [15].

TCM classifies depression into liver Qi stagnation type, liver depression and spleen deficiency type, deficiency of both heart and spleen, etc., according to the different types of TCM syndrome [16]. The classic TCMPs corresponding to the different types of TCM syndrome include Yueju Wan; Xiaoyao San and Pinellia and Magnolia Decoction; and Guipi Decoction and GanMaiDazao Decoction. Each TCMP is a combination of different herbs in TCM. The aforementioned TCMPs have been compiled and their specific compositions can be found in Table 1. In practice, TCMPs can be added or subtracted from the original TCM composition or combined with acupuncture and topical treatments. Most TCM contain various antidepressant agents, including flavonoids, terpenoids, phenylpropanoids, quinones, and alkaloids. This paper reviews the pharmacological mechanisms of TCMPs for treating depression and summarizes the progress of clinical research on using classical TCMPs for depression treatment.

2.1. Improvement of neurobiochemical abnormalities

Neurobiochemical abnormalities in patients with depression are mainly manifested in abnormal expression levels of neurotransmitters and their receptors, changes in neuronal plasticity and related signaling pathways, abnormal secretion of inflammatory factors, and disorders of the hypothalamic-pituitary-adrenal (HPA) axis, etc. TCMPs can be used to treat depression by improving neurobiochemical abnormalities.

2.1.1. Improvement of neurotransmitter and its receptor expression levels

Current research on depression and neurotransmitters focuses on the expression of monoamine neurotransmitters such as 5-HT, NE, and DA, peptide neurotransmitters such as substance P and neuropeptide Y, and amino acid neurotransmitters such as glutamate and

aspartate, and their associated receptors. The neurotransmitter hypothesis proposes that depression development is closely linked to reduced levels, abnormal functioning, and decreased sensitivity of neurotransmitters and their receptors within the central nervous system. In recent years, with the deepening of research on the TCMPs to regulate neurotransmitters to improve depression, some research results have now been achieved. Zhang et al. established a perimenopausal depression model in mice by performing ovariectomy combined with chronic unpredictable mild stress (OVX-CUMS) and administering XCHD doses via continuous gavage. The data confirmed that XCHD mitigated perimenopausal depression-like behaviors and restored HPA/hypothalamic-pituitary-ovary (HPO) axis functions in 5-HT and OVX-CUMS mice. Mechanistically, these effects were possibly associated with the upregulated expression of estrogen receptor-n and recombinant tryptophan hydroxylase 2 (TPH2) in the prefrontal cortex and hypothalamus [44].Yan et al. observed the effect of Yueju Wan on a mouse model of chronic mild unpredictability (CUMS) [17]. They found that Yueju Wan could increase the 5-HT content in the brain tissue of CUMS mice; In another experiment, they compared the brain 5-HT content of CUMS mice in the Yueju Wan group with that of the amitriptyline group and found that there was no significant difference between the two groups, confirming that the efficacy of Yueju Wan in increasing brain 5-HT content of CUMS mice was comparable to that of amitriptyline [17]. The results showed that there was no significant difference between the two groups, confirming that the efficacy of Yueju Wan in increasing the 5-HT level in the brain of CUMS mice is comparable to that of amitriptyline, and suggesting that Yueju Wan may exert its antidepressant effect by increasing the level of 5-HT in the brain. Furthermore, a clinical trial demonstrated that Yueju Wan have similar antidepressant effects to escitalopram and are effective in treating depression characterized by deficiency syndrome [45]. Yi et al. found that among all the dosage groups of Pinellia and Magnolia Decoction, the null dose of Pinellia polysaccharides and the effective dose of Magnolia phenol mixture produced a significant synergistic effect, which was able to increase the levels of 5-HT and DA in the frontal cortex of the model mice [46].

Research has shown that ginsenoside Rg1 can regulate glutamate content and inhibit its receptor expression in the brain of CUMS rats [47]. Additionally, Wang et al. found that ginsenoside Rb1 can also have an antidepressant effect by affecting hippocampal 5-HT levels and 5-HT1A receptor expression [48]. The study found that dopamine (DA) concentrations in the hippocampal region and striatum of model mice were significantly increased by gavage administration of inulin pentasaccharide, hexasaccharide, heptasaccharide, and nesquiterpene at a dose of 800 mg-kg^{-1} [49]. Another study showed that Zhimenoside B II at a dose of 150 mg-kg^{-1} significantly enhanced the neurological effects of 5-HT and DA in the brain [50]. Liu et al. used ovariectomized perimenopausal mice as a research model and injected 30 mg kg^{-1} of betaine intraperitoneally [51]. This resulted in significant activation of 5-HT receptors and amelioration of depressive-like behaviors in the model mice.

The results suggest that certain classical TCMPs are as effective as WM in treating depression. And that these TCMPs and some of the monomeric compounds they contain most likely exert their antidepressant effects by improving brain neurotransmitter levels or receptors.

2.1.2. Regulation of neuronal plasticity and related pathways

Neuronal plasticity, also known as brain plasticity, refers to the ability of the central nervous system (CNS) to change its morphological structure and functional activity under certain conditions. This includes the ability to develop a differentiation from the normal pattern or specificity, which can result in neuronal and neuroglial cell damage and impaired intra-neuronal signaling pathways [52]. The reduction in the number of nerves in the brain or the associated atrophy of important intracerebral tissues, which is the main reason for the altered neuronal plasticity that leads to depression. A vital component of the brain's limbic system, the hippocampus is sensitive and vulnerable to chronic stress. Its role in regulating mood-related neurofactor secretion has been extensively studied in neurological disorders. Structural damage to hippocampal neurons and altered neuronal plasticity, particularly atrophy and loss of hippocampal neuronal dendritic cells, may be the primary factors leading to depression. Depression-mediated hippocampal neuronal plasticity damage is associated with brain-derived neurotrophic factor (BDNF) expression [53]. Binding of BDNF to its receptor, the tyrosine kinase receptor B (TrkB) protein, can activate depression-related signaling pathways and regulate related trophic proteins. It also can ameliorate brain neuronal atrophy, increase the number of nerves in the hippocampal region of the brain, which promotes neuronal excitability and regulates the organism's psycho-spiritual state.

Relatively few studies have been conducted on TCM in regulating and enhancing neuroplasticity and related pathways, due to the complexity of the pathways in depression. Li et al. conducted a study on the impact of WLC (Wuling Capsule) on BDNF, neuroregeneration, and connexin 43 (Cx43) expression in the hippocampal dentate gyrus of a CUMS depression rat model. The findings revealed that BDNF positive expression, new cell numbers, and Cx43 mRNA and protein expression levels in the dentate gyrus of chronically stressed rats were significantly reduced compared to normal rats. Following WLC treatment, depressive behaviors in rats improved, abnormal hippocampal nerve regeneration was restored, and Cx43 mRNA and protein expression normalized; however, there was no significant change in BDNF expression [54]. Furthermore, ZhiZiHouPo Decoction (ZZHPD) effectively eased depression-like behaviors induced by CUMS and boosted hippocampal neurogenesis through the modulation of immature and mature neurons in the DG (dentate gyrus) region. This was attributed to an elevation in the levels of BDNF and monoamine neurotransmitters in the hippocampus [55].

The study found that Shuyu granules, a proprietary TCM, increased the content of BDNF in the hippocampus and ameliorated the neuronal changes in the hippocampus of CUMS rats [56]. Yueju Ganmai Dazao Decoction was found to regulate and improve depressive-like behaviors, which by modulating the protein kinase A (PKA)/cyclophosphoadenosine effector-binding protein (CREB)/BDNF signaling pathway in model mice and increasing BDNF expression [57]. Lily of the valley and motherwort soup, among others, can increase the expression of BDNF and TrkB proteins in the hippocampus of CMUS rats and ameliorate the depressive-like behaviors of CUMS rats [58]. It is important to note that these findings are based on animal studies and further research is needed to determine their applicability to humans. Compound ChaiJin YiYu Tablet (CJJYT) has been shown to improve synaptic function and

have a significant protective effect on hippocampal neurons in both in vitro and in vivo experiments. This can repair structural damage and improve cognitive ability in CUMS rats. The improvement may be related to the transmission and function of SYN-α/NR and its downstream neurotransmitters [59].

The study of Suanzaoren Decoction showed that its flavonoids (spironolactone and 6-feruloyl-spironolactone), saponins, and alkaloids can prolong patients' sleep time, improve sleep quality, and have sedative and hypnotic effects [60,61]. The triterpenoids can inhibit the release of Glu, reduce the 5-HT and NE content in the hippocampus of rats, and inhibit the transmission of excitatory signals. This produces central inhibition and results in sedative-hypnotic effects [20,62,63]. Meanwhile, it was found that Suanzaoren Decoction increased the expression of BDNF and its receptor TrkB in the hippocampus of CMUS rats, as well as the secretion of neurotransmitters such as 5-HT, DA, and NE. It also regulated the JAK2/STAT3 and cAMP-PKA-CREB signaling pathways, and reduced the concentration of inflammatory factors IL-6, IL-1β, and TNF-α in serum and hippocampus. The study found that the intervention decreased the expression of glutamate receptors NMDAR2A and NMDAR2B, while increasing the.expression of GluR1, CaMKIIα, and β-catenin genes. Additionally, it reduced the expression of protofibrillar and gap junction proteins in cerebral cortex glial cells. These changes resulted in improved neurological function and enhanced synaptic plasticity, ultimately leading to an antidepressant effect [19,64,65]. We have summarized the mechanism of action of Suanzaoren decoction as an antidepressant and shown it in Fig. 1.

In conclusion, many TCMPs have the ability to increase neuronal plasticity and modulate multiple signaling pathways and related proteins. Which may contribute to their antidepressant effects, and have a therapeutic advantage over single WM in that they may achieve their antidepressant effects through multiple pharmacological actions and signaling pathways.

2.1.3. Inhibition of secretion of inflammatory factors

Inflammatory cytokines can be divided into pro-inflammatory cytokines and anti-inflammatory cytokines, and their abnormal secretion can also cause depression and is often accompanied by an immune activation response. The level of inflammatory factors in the body changes after chronic stress, and the expression level of interleukin-1 (IL-1), interleukin-6 (IL-6), interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), are significantly increased in the serum, which causes toxic effects to the nervous system, destroys nervous cells and damages associated neurons [66]. Overexpression of pro-inflammatory factors may be associated with decreased

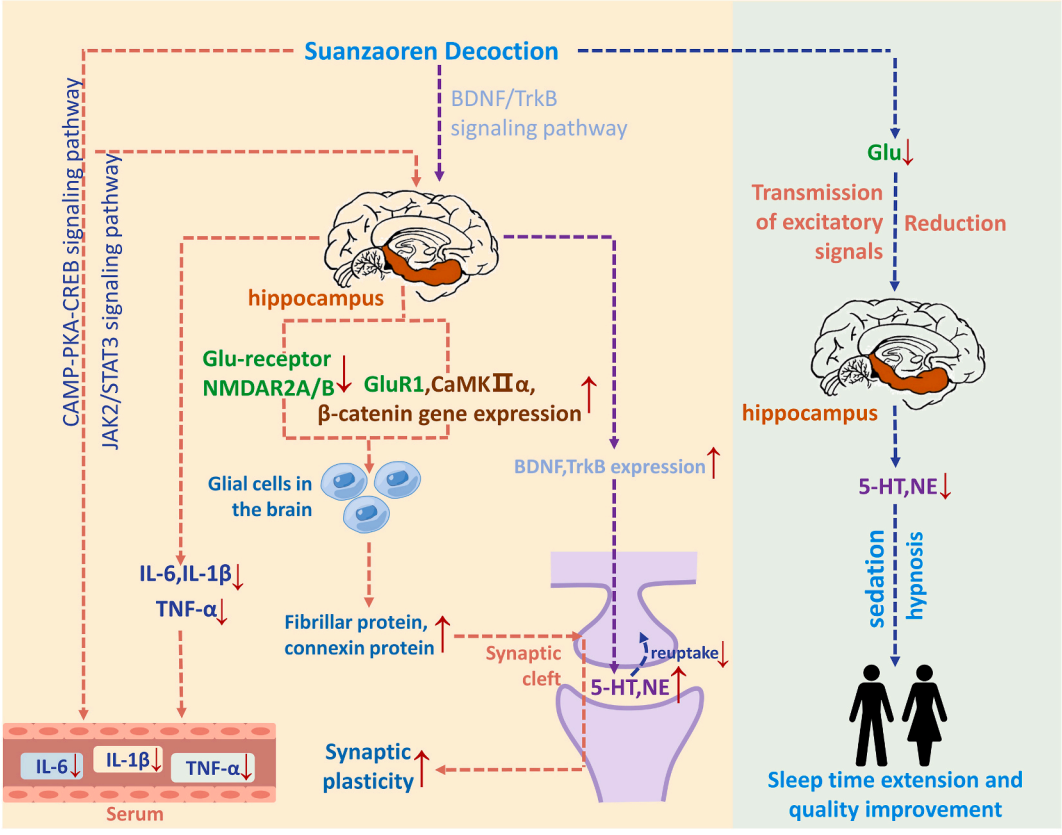

Fig. 1. Mechanism of antidepressant effect of Suanzaoren Decoction. Notes: CAMP: Cyclic Adenosine monophosphate; PKA: Protein kinase A; CREB: cAMP-response element binding protein; JAK2: Janus kinase-2; STAT3: Signal transducer and activator of transcription-3; IL-6: Interleukin-6; IL-1β: Interleukin-1β; TNF-α: Tumor necrosis factor-α; BDNF: Brain-derived neurotrophic factor; TrkB: Tyrosine kinase B; Glu: Glutamate; NMDAR2A/B: N-Methyl-D-Aspartate 2A/B; GluR1: Glutamate receptor 1; CaMKIIα: Calmodulin Dependent Protein Kinase II Alpha; 5-HT: 5-hydroxytryptamine; NE: Norepinephrine.

5-HT, abnormal HPA axis activation, and functional brain changes [67].

More and more studies have found that TCMPs can play an antidepressant role by blocking the activation of inflammatory pathways, reducing the expression level of inflammatory factors, and restoring the function of anti-inflammatory factors, as well as promoting neuron regeneration, increasing neuron activity, and regulating and improving neurotransmitter levels. Mahuang-Fuzi-Xixin Decoction (MFX) demonstrates antidepressant-like effects in lipopolysaccharide (LPS)-induced mice by regulating neurogenesis. This effect may be attributed to the inhibition of nucleotide-binding oligomerization domain, leucine rich repeat, and pyrin-domain containing protein 3 (NLRP3) inflammasome activation and the reduction of BDNF expression [68]. Salvianolic acid B, a polyphenolic compound isolated from Salvia miltiorrhiza, demonstrates antidepressant-like effects in mice with chronic mild stress (CMS) and has the ability to enhance hippocampal neurogenesis by promoting the polarization of inflammation-mediated microglial M2 in both the hippocampus and cortex [69]. These studies have demonstrated that an overabundance of pro-inflammatory cytokines can cause significant damage to hippocampal neurogenesis. TCMPs have been shown to promote neurogenesis by reducing the inflammatory response in the hippocampus and increasing levels of anti-inflammatory cytokines.

The concentrated medicinal solution of each dose group of Lily and Rehmannia Decoction combined with Suanzaoren Decoction could accelerate the weight gain of CUMS rats, improve their behavioral performance, enhance their vertical and horizontal movement ability, and effectively reduce the serum levels of IL-1, IL-6, and TNF-α. This suggests that Lily and Rehmannia Decoction combined with Suanzaoren Decoction may have an antidepressant effect by regulating the release of pro-inflammatory factors [70]. Jiaotai Wan upregulated the expression of anti-inflammatory cytokines IL-4 and IL-10, and downregulated the expression of IL-1β, IL-6, and TNF-α in the serum and hippocampus of CUMS rats [71]. Likewise, Jiawei Sini San reduced the expression levels of IL-1β, IL-2, IL-6, and TNF-α, modulated the HPA axis, and improved immune cell function [72].

Xiao Chaihu Decoction, a TCMP in the Treatise on Typhoid Fever, has been used to treat depression. Saikosaponin A, at various doses, was found to improve perimenopausal pleasure deficit and despair-like depressive-like behaviors in rats. Additionally, it downregulated the expression levels of IL-1β, IL-6, and TNF-α [73]. Astragalus polysaccharide was found to reduce the expression level of inflammatory factors by inhibiting the inflammatory nuclear transcription factor-κB (NF-κB) signaling pathway [74]. In addition, kaempferol was found to reduce the levels of inflammatory factors IL-1β and TNF-α and to attenuate neuronal damage by inhibiting neuronal autophagy and oxidative stress [75]. TCMPs and the monomeric compounds they contain may have antidepressant effects by inhibiting the inflammatory response signaling pathway, reducing the expression of pro-inflammatory factors, and increasing the expression of anti-inflammatory factors.

2.1.4. Modulation of the HPA axis

The HPA axis is an endocrine axis that can maintain internal homeostasis and stress response. It has important regulatory functions that control the secretion of a variety of regulatory peptides and hormones, participate in a variety of stress responses, and regulate in vivo activities. Neuroendocrine studies have revealed hyperactivity of the HPA axis in individuals with major depression, a correlation between HPA axis activity and cognitive function, as well as a potential impact of genetic variations in the HPA axis on cognition [76]. When the body perceives exogenous stimuli, the HPA axis is radicalized, and the adrenal gland secretes increased levels of corticosterone (CORT), in order to stimulate the body to adapt to the new environment. Clinical studies have shown that patients with depression are often accompanied by hyperfunction of the HPA axis, which is mainly manifested by increased levels of hormones such as corticotropin-releasing hormone (CRH) and glucocorticoids (GC) [77]. GC attacks the hippocampus, which is rich in the GR of glucocorticoids, resulting in stress damage. And then triggers the dysfunction of the body's endocrine, immune, neurological, and other multi-systems, seriously affecting the body's normal function and promoting the development of diseases [36].

Many CCMs have been shown to ameliorate depression-like behavior by promoting hippocampal neurogenesis by regulating the HPA axis. ZZHPD significantly ameliorated the depressive-like behaviors, normalized the levels of adrenocorticotropic hormone (ACTH) and CORT, restored the negative feedback loop of HPA axis, and improved the levels of BDNF, DCX, and BrdU/NeuN compared with those in CUMS-induced rats [78]. Moreover, XYS improved CUMS-induced rat's body weight, food intake, and depressive-like behavior. Studies also proved that XYS could reverse the CUMS-induced changes of the CORT of HPA axis and affect the astrocytic activities and down-regulate the NR2B subunit of NMDA receptor (NR2B) level in the hippocampus [79].

In the study of the regulation of the HPA axis, TCMPs to improve depression has also made some progress. Liu Yueyun found that Xiaoyao San can significantly reduce CORT and ACTH content, significantly increase corticotropin-releasing hormone (CRH) content, and significantly regulate HPA axis alteration in rats with liver depression and spleen deficiency type [80]. Zhu et al. showed that CORT and urinary corticotropin 2 (UCN2) levels were not only upregulated, but corticotropin-releasing hormone receptor 2 (CRHR2) levels were also downregulated in CUMS model rats [21]. This ameliorated the overactivation of the HPA axis. Furthermore, studies have shown that TCMPs such as Chaiyue Decoction [81], Kidney and Liver Tonifying formula and Lily of the Valley Liver Sparing and Calming Decoction can exert their antidepressant effects by modulating receptors and proteins related to the HPA axis [36,82].

2.2. Microenvironmental improvement of intestinal flora

Human intestinal microbiota is abundant, diverse and complex, and the intestinal flora is mainly divided into three categories: normal bacteria, harmful bacteria and conditionally pathogenic bacteria. The occurrence of many diseases is associated with the dysfunction of intestinal flora. The dysfunction of flora leads to the invasion of harmful pathogenic bacteria, which damages the intestinal mucosal barrier. The damaged intestinal mucosal barrier increases the possibility of the body to be infected with pathogenic bacteria, and results in metabolic dysfunction, which leads to the occurrence of diseases [83,84]. In recent years, the composition of the intestinal flora has become a research hotspot in depression research. Studies have used 16S rRNA gene sequencing technology to

compare the composition of microorganisms in the intestines of 58 patients with depression and 63 healthy people. Significant differences were found, with patients with depression having a significant increase in the number of pathogenic bacteria in the intestinal tract [85]. Research has shown that lactobacilli and bifidobacteria can relieve depression by altering the composition and diversity of the gut microbiota, reducing inflammatory factors, and regulating the central nervous system [86], suggesting that lactobacilli and bifidobacteria can be used as an adjunct to the clinical treatment of depression.

After oral administration, the majority of TCMPs is absorbed through the gastrointestinal tract, directly impacting the composition and metabolism of gut flora. This subsequently influences brain function. CUMS, restraint stress, and CORT stimulation all result in dysfunction in the microbiota-gut-brain axis (MGB axis) and trigger mental illness. The interaction between gut microbiota and depression occurs through the "brain-gut-microbe" axis [87,88]. This interaction occurs in three main ways.

Firstly, the intestinal flora influences the level of inflammatory factors. The linchpin of the association between gut flora and brain is mainly the cholinergic anti-inflammatory pathway. As an important inflammatory anti-inflammatory pathway in the organism, it can prevent and control a variety of neurological disorders by modulating systemic or local inflammation or by reducing the inflammatory response [89]. There has been evidence that Xiaoyao San (XYS) can alleviate anxiety and depressive-like symptoms in Antibiotic-Induced Microbiome-Depleted mice by modulating intestinal flora, correcting excessive lipopolysaccharide release, and inhibiting overactivation of NLPR3 inflammatory vesicles in the colon [90]. Zhu et al. conducted a study to investigate the effects of XYS on depressive behaviors using intestinal flora. A total of 52 healthy male Sprague-Dawley rats were randomly assigned to four groups: control, model, XYS, and fluoxetine. The latter three groups underwent 21 days of chronic restraint stress to establish a stress/depression model. The study findings revealed that XYS regulated the abundance of Bacteroidetes, Proteobacteria, Firmicutes, Chloroflexi, and Planctomycetes. Additionally, XYS increased the abundance of Ruminococcaceae family to ameliorate depression-like behaviors. These mechanisms are potentially associated with short-chain fatty acids, lipopolysaccharides, and intestinal inflammation [91]. Similar results were reported in studies of herbal schisandrin extracts [92], which significantly ameliorated ecological gut dysbiosis and reduced levels of pro-inflammatory factors in depressed mice, most likely by inhibiting TLR4/NF-κB pathway expression.

The second is the effect of the gut flora on the HPA axis and on the hippocampus. Intestinal flora disorders are likely to cause HPA axis hyperactivity and abnormalities in hippocampal organization and protein expression. By nourishing hippocampal neurons, influencing neurotransmitter metabolism, reducing HPA axis hyperactivity, improving hippocampal tissue structural defects, altering the content of Bifidobacterium spp., Roseburia spp., Corynebacterium glutamicum spp. and Lactobacillus spp. at the genus level,

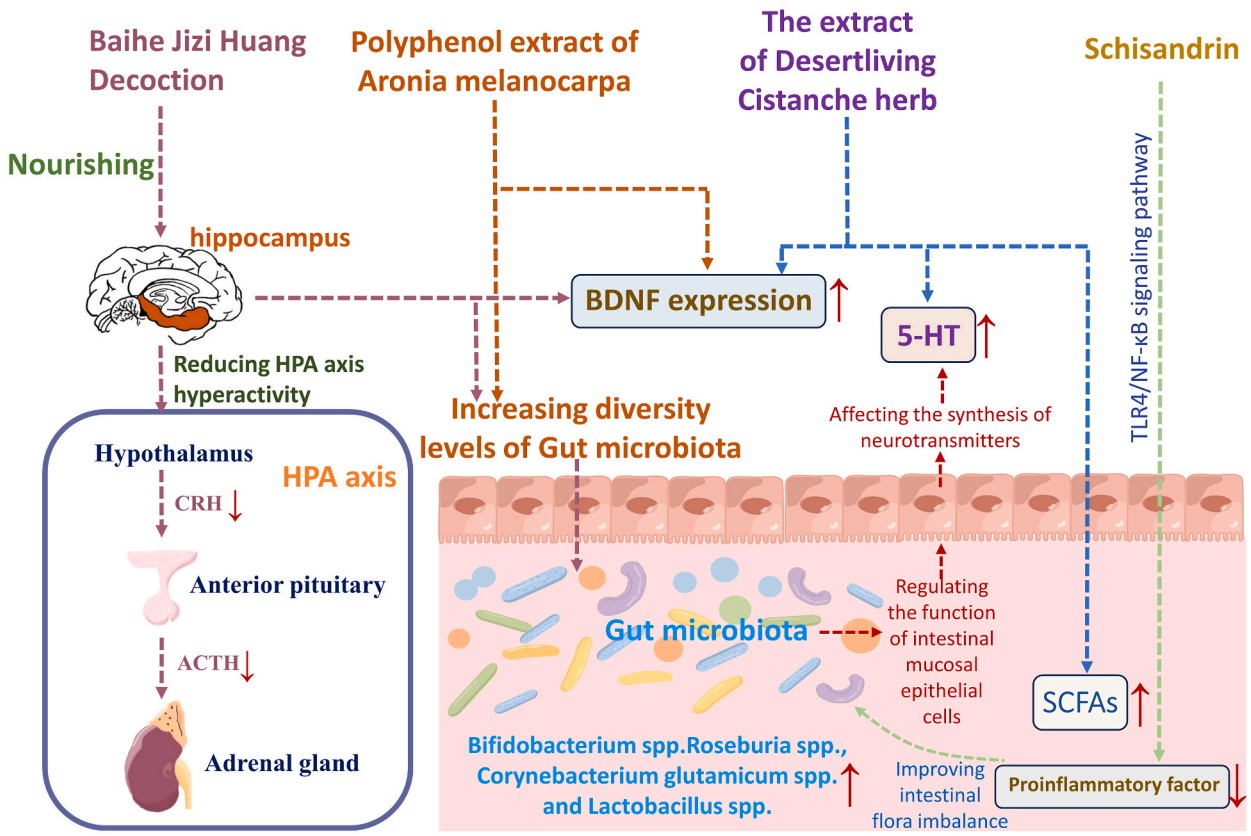

Fig. 2. Mechanism of Baihe Jizihuang Decoction and extracts of several TCM on intestinal flora and HPA axis. Notes: HPA axis: The hypothalamic–pituitary–adrenal axis; CRH: Corticotropin releasing hormone; ACTH: Adrenocorticotropic hormone; BDNF: Brain-derived neurotrophic factor; 5-HT: 5-hydroxytryptamine; SCFAs: Short-chain fatty acids; TLR4: Toll-like receptor-4; NF-κB: Nuclear factor-k-gene binding.

regulating BDNF expression in the hippocampus of CUMS rats, and correcting intestinal flora deficiencies, Baihe Jizihuang Decoction has improved the depressive-like behaviors of CUMS mice [93]. In mice subjected to restraint stress-induced depression, Chaihu Shugan San demonstrates antidepressant effects by increasing the abundance of Lactobacillaceae and Prevotellaceae, reducing the abundance of γ-Proteobacteria, inhibiting NFκB-activated IL-6 expression, and enhancing BDNF expression [94]. Polyphenol extracts from Aronia melanocarpa leaves and fruits can significantly increase intestinal flora diversity and promote BDNF expression in the brain of depressed mice [95], exerting its antidepressant effect and providing a new resource for dietary modification of depression.

Thirdly, the influence of intestinal flora on neurotransmitters. The gut flora can affect neurotransmitter production by regulating the function of intestinal mucosal epithelial cells. In additional, the commensal microorganisms in the human gut can directly synthesize or secrete neurotransmitters, such as GABA and DA. These neurotransmitters activate stress loops through the vagus nerve and circulatory system, directly affecting the function of the central nervous system [96]. Intestinal chromaffin cells produce more than 90 % of the human 5-HT in the gastrointestinal tract. According to Wikoff et al. [96], germ-free mice had significantly lower serum concentrations of 5-HT compared to normal mice. A study demonstrated that the extract of Desertliving Cistanche herb can significantly increase 5-HT levels and BDNF expression in the hippocampus of CUMS rats, regulate the disruption of intestinal flora, and the level of metabolite SCFA to exert antidepressant effects [97]. We have summarized the mechanism of Baihe Jizihuang Decoction and extracts of several TCM on intestinal flora and HPA axis in Fig. 2. Additionally, gut flora can convert glutamate to amino butyric acid to alter neurotransmitter levels [86]. Lactobacillus and Bifidobacterium can use monosodium glutamate to synthesize the inhibitory neurotransmitter GABA, which has an effect on the central nervous system. PolygalaeRadix extract can significantly increase the levels of NE and 5-HT in hippocampal tissues, decrease the levels of ACTH and CORT in serum, attenuate the hyperfunctioning of the HPA axis, and restore the homeostasis of the intestinal flora to exert an antidepressant effect [98].

TCMPs need to be decocted before consumption, and the soup then undergoes a series of gastrointestinal digestion and absorption metabolism processes. The findings suggest that antidepressant TCMPs may regulate intestinal microorganisms, affecting the patients' nervous system, improving their depressive state, and regulating their mood [99].

2.3. *Improvement of mitochondrial energy metabolism*

Mitochondria are organelles found in eukaryotic cells that are responsible for energy production and play a critical role in maintaining cell stability by regulating calcium homeostasis, controlling the production of reactive oxygen species, and regulating apoptosis. Studies have shown that patients with depression have altered and abnormal mitochondrial structure and function. Some researchers have proposed that mitochondrial energy metabolism disorders may be a pathogenic mechanism of depression [100–102]. Depressed patients have persistent low mood and fatigue as major clinical features. Abnormal mitochondrial function reduces ATP synthesis [103], leading to depression. Firstly, Disturbances in mitochondrial energy metabolism leading to depression because of abnormalities in the morphology and structure of the mitochondria [104,105]. Secondly, the mitochondrial membrane potential decreases, resulting in the termination of ATP synthesis in the hippocampus, a decrease in ATP content, and apoptosis of neuronal cells [106]. Thirdly, mitochondrial damage impairs synaptic plasticity, and synaptic dysfunction worsens the degree of depression [107].

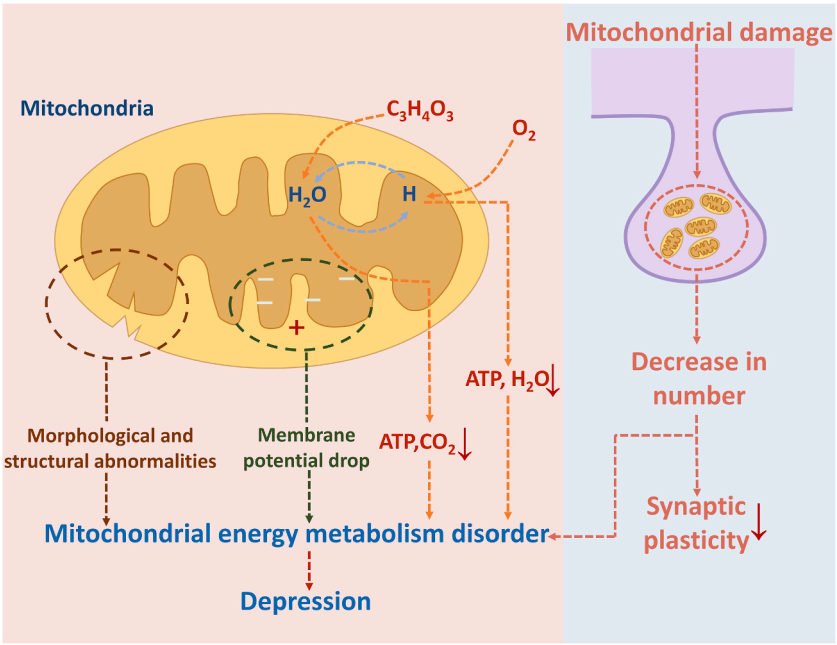

Fig. 3. Mechanisms of mitochondrial metabolic energy disorders leading to depression. Notes: ATP: Adenosine Triphosphate.

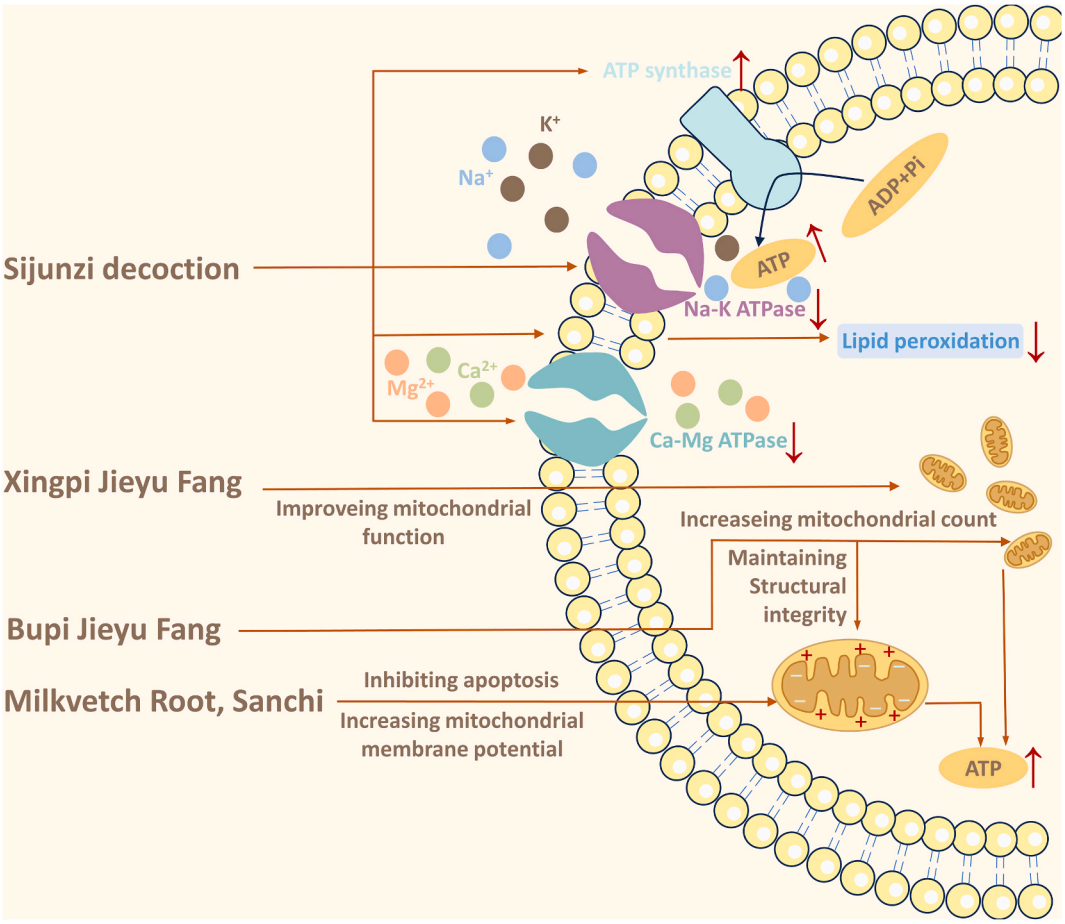

Fig. 4. The mechanisms of Sijunzi Decoction, Bupi Jieyu Fang, Xingpi Jieyu Fang, Milkvetch Root, Sanchi to improve mitochondrial energy metabolism disorders. Notes: ATP: Adenosine Triphosphate; ADP: Adenosine diphosphate.

We have mapped the mechanism by which mitochondrial energy disorders lead to depression in Fig. 3.

In recent years, there have been many studies on the treatment of mitochondrial energy metabolism disorders in depression with TCMPs. It has been found that strengthening the spleen and benefiting the Qi can significantly improve the psychiatric and somatic symptoms of depressed patients by improving mitochondrial energy metabolism disorders. Sinisan has been shown to alleviate depression-like and anxiety-like behaviors in MS (maternal separation) rats. Additionally, it has been found to improve synaptic and mitochondrial damage, reduce the decrease of ATP in the hippocampus, and reverse the expression levels of PSD-95 (postsynaptic density 95), SYN (synuclein), Mfn2 (mitofusin 2), Drp1 (dynamin-related protein 1), and Fis1 (fission 1) proteins [108]. Junzi Tang found that in the skeletal muscle of rats with splenomegaly, it can significantly enhance mitochondrial ATPase activity, decrease Na–K-ATPase and Ca–Mg-ATPase activities, decrease lipid peroxidation, attenuate mitochondrial oxidative damage, and regulate the energy metabolism of the organism. Ding et al. suggested that depression is caused by spleen deficiency and energy metabolism disorders [109]. They proposed to regulate energy metabolism by using RenCan JianPi Wan and Guipi Decoction to prevent and treat depression. Li et al. found that Xingpi Jieyu Fang could significantly improve mitochondrial function and increase ATP content in CUMS rats [110]. Scientists have had a similar study on depression in connection with liver depression and spleen deficiency type [111]. After treatment with Bupi Jieyu Fang, model rats showed a significant increase in the number of mitochondria in prefrontal cells and hepatocytes. The mitochondria were densely distributed, had an intact matrix, and exhibited normal morphology and structure. These findings suggest that tonifying the spleen and regulating Qi can alter the structural function of mitochondria, regulate energy metabolism, and ultimately produce an antidepressant effect. Furthermore, it has been reported that when Astragalus and Panax ginseng are combined, their main components can increase mitochondrial membrane potential, accelerate ATP synthesis, inhibit apoptosis, and maintain normal cellular physiological function [112]. We have summarized the mechanisms of Sijunzi Decoction, Bupi Jieyu Fang, Xingpi Jieyu Fang, Milkvetch Root, Sanchi to improve mitochondrial energy metabolism disorders in Fig. 4.

3. Conclusion and prospects

The treatment of depression remains a major challenge for modern medicine due to a lack of understanding of its pathogenesis, and

existing treatments have not been successful in halting or reversing the progression of depression at an early stage. TCMPs have long been under clinical investigation for their efficacy in the treatment of depression. This article reviews the antidepressant mechanisms of classic TCMPs by examining their clinical research and mechanism of action, including improving neurotransmitter levels, regulating inflammatory factors, balancing the HPA axis, increasing brain-derived neurotrophic factors, enhancing neural plasticity, and improving intestinal flora disorders.

The field of TCM boasts a rich history and extensive expertise in addressing depression. It has fewer side effects than WM, which makes it an advantage in this regard. Moreover, TCM does not produce drug tolerance. Taking Suanzaoren Decoction as an example, it can affect the levels of neurotransmitters and inflammatory factors in the body through CAMP/PKA/CREB, JAK2/STAT3, BDNF, and other pathways, thus improving the patient's depressive state. This indicates that TCMPs has multi-mechanism and multi-pathway characteristics, which is consistent with its multicomponent structure. Similarly, the characteristics of multicomponent, multi-mechanism, and multipathway also bring certain difficulties to their in-depth study.

Previous studies on the treatment of depression in TCM have been limited and have not fully understood the etiology and pathogenesis of depression, and there is no widely accepted and effective treatment plan.

In conclusion, a deeper understanding of the scientific connotation of TCM in the treatment of depression can be gained by closely combining TCM theory and clinical practice, fully utilizing neuroscience and biology methods, and conducting multidisciplinary and multimodule system integration research. This can accelerate the modernization process of TCM and promote its research and application in clinical practice.

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Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Yiwei Chen: Writing – original draft. **Ruyu Wang:** Writing – review & editing. **Xue Li:** Writing – review & editing. **Zhiying Wang:** Writing – review & editing. **Baorui Cao:** Writing – review & editing. **Jinxin Du:** Writing – review & editing. **Tingting Deng:** Writing – review & editing. **Jinxiang Han:** Writing – review & editing. **Meina Yang:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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