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The pharmacotherapy of depression - searching for new mechanisms and drug interactions. Basic and clinical research, volume II

Edited by
Katarzyna Stachowicz, Magdalena Sowa-Kucma and Anna Tabęcka-Łonczynska

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The pharmacotherapy of depression - searching for new mechanisms and drug interactions. Basic and clinical research, volume II

Topic editors

Katarzyna Stachowicz — Maj Institute of Pharmacology, Polish Academy of Sciences, Poland

Magdalena Sowa-Kucma — University of Rzeszow, Poland

Anna Tabęcka-Łonczynska — University of Information Technology and Management in Rzeszow, Poland

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EDITED AND REVIEWED BY
Nicholas M. Barnes,
University of Birmingham, United Kingdom

*CORRESPONDENCE
Katarzyna Stachowicz,
stachow@if-pan.krakow.pl

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Editorial: The pharmacotherapy of depression-searching for new mechanisms and drug interactions. Basic and clinical research, volume II

Katarzyna Stachowicz[1]*, Magdalena Sowa-Kućma[2] and Anna Tabecka-Łonczyńska[3]

[1]Department of Neurobiology, Maj Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland, [2]Department of Human Physiology, Institute of Medical Sciences, Medical College of Rzeszow University, Rzeszow, Poland, [3]Department of Biotechnology and Cell Biology, Medical College, University of Information Technology and Management in Rzeszow, Rzeszow, Poland

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Editorial on the Research Topic
The pharmacotherapy of depression-searching for new mechanisms and drug interactions. Basic and clinical research, volume II

The second edition of the e-book "*The pharmacotherapy of depression-searching for new mechanisms and drug interactions*" includes research and review papers.

Three Reviews present the mechanisms of autophagy, ferroptosis, and mitophagy as a new strategy for treating depression (Lv et al.; Zhang et al.; Xu et al., respectively).

Autophagy is a crucial mechanism of intracellular degradation, while ferroptosis is a form of cell death caused by excessive accumulation of iron-dependent lipid peroxides. The importance of these two cellular processes in developing and treating depression has been extensively discussed by Lv et al. and Zhang et al., respectively. The authors presented basic information about autophagy and ferroptosis and the possible connections between these processes and depression. Furthermore, the importance of these processes in response to classical antidepressants (e.g., fluoxetine, agomelatine, ketamine) and active ingredients derived from Traditional Chinese Medicine (TCM) have been widely discussed. Various strengths, limitations, and research prospects targeting autophagy and ferroptosis in depression have been highlighted.

Mitophagy is the process of removing excess or dysfunctional mitochondria. Disturbances in the proper course of mitophagy are associated with the progression of depression. To date, presented results have allowed the creation of new pharmacological strategies that may stimulate mitophagy and, at the same time, alleviate depression. It was observed that several antidepressants, such as fluoxetine and ketamine, as well as compounds used in TCM (baicalin), brought good therapeutic results related to the induction of mitophagy (Xu et al.). Further comprehensive research, therefore, brings great hope for the use of innovative therapies to treat depression.

Also, new potential antidepressants and their molecular targets are presented in this e-book. Ye et al., using a maternal separation with an early weaning model [early life stress

(ELS) model - the leading risk factor for depression in teenagers), demonstrated the antidepressant-like effect of the Si-Ni-San formula (SNS - a fundamental prescription for treating depression in TCM) in three primary tests (sucrose preference test, forced swim test, tail suspension test) for examining the antidepressant activity of compounds in mice. The observed behavioral alterations were strongly related to RAS-related C3 Botulinum Toxin Substrate 1 (Rac1) activity and associated spine plasticity in the NAc (Ye et al.).

Substantial evidence for the effectiveness and safety of quinolone in the treatment of major depressive disorder (MDD) is provided by a systematic review by Wang et al. This neuroactive steroid (NAS) and GABA-A receptor-positive allosteric modulator (PAM) was approved by the FDA as the first oral treatment for postpartum depression, and its effectiveness in this disorder is well documented. The presented meta-analysis, including 4 studies involving a total of 1,454 patients, shows fate of quinolone research in MDD treatment (Xu et al.). Furthermore, Dudek et al. showed that the efficacy of trazodone (a serotonin 5-HT2 receptor antagonist and reuptake inhibitor) in patients with MDD administered in an extended-release form was comparable to or even superior to SSRIs.

However, it is essential to analyze adverse events associated with the use of antidepressants. Here, adverse events associated with the use of antidepressants along with adaptogens were described (Siwek et al.). Nearly 9% of adverse events are due to the use of antidepressants with other medications, so following the author's suggestion, the clinic should consider better monitoring of the medications patients are taking to avoid side effects and pharmacological interactions (Siwek et al.). Successively, sertraline used as an antidepressant was found to be involved in increasing thioflavin-S and Congo red deposition in APPswe/PSEN1dE9 mice (Liao et al.). The changes were connected with hippocampus gliosis and decreased recognition index in APP/PSEN1 mice (Liao et al.). These studies indicate the need to monitor the use of sertraline in patients with Alzheimer's disease (AD) and co-morbid depression.

Increasingly, scientists are paying detailed attention to Chinese medicine. It is also used in the treatment of depression. Interestingly, the effectiveness and safety of Chinese herbal medicines in antidepressant therapy were assessed using meta-analysis. The results were compared with standard pharmacotherapies by searching multiple databases with research results. As shown, traditional medicines such as fluoxetine, escitalopram, amitriptyline, sertraline, flupentixol, melintracene, and venlafaxine are less effective and have a higher risk of adverse symptoms than Chinese herbal medicines. Therefore, it seems that the potential of Chinese herbs may be an effective alternative to classic therapeutic procedures in the treatment of depression. However, long-term studies in patients are needed to confirm effectiveness and safety (Chun et al.).

Author contributions

KS: Writing–original draft, Writing–review and editing. MS-K: Writing–original draft, Writing–review and editing. AT-L: Writing–original draft, Writing–review and editing.

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EDITED BY
Katarzyna Stachowicz,
Polish Academy of Sciences, Poland

REVIEWED BY
Tomasz Sobow,
University of Łódź, Poland
Marek Krzystanek,
Medical University of Silesia, Poland

*CORRESPONDENCE
Marcin Siwek,
marcin.siwek@uj.edu.pl

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Harder, better, faster, stronger? Retrospective chart review of adverse events of interactions between adaptogens and antidepressant drugs

Marcin Siwek[1]*, Jarosław Woroń[2,3,4], Anna Wrzosek[3,5], Jarosław Gupało[6] and Adrian Andrzej Chrobak[7]

[1]Department of Affective Disorders, Chair of Psychiatry, Jagiellonian University Medical College, Kraków, Poland, [2]Department of Clinical Pharmacology, Chair of Pharmacology, Faculty of Medicine, Jagiellonian University Medical College, Kraków, Poland, [3]Department of Anesthesiology and Intensive Care, University Hospital in Cracow, Kraków, Poland, [4]University Center for Monitoring and Research on Adverse Drug Effects in Krakow, Kraków, Poland, [5]Department of Interdisciplinary Intensive Care, Jagiellonian University, Krakow, Poland, [6]Pharma Consult, Pharmacotherapy Safety Team, Zakopane, Poland, [7]Department of Adult Psychiatry, Chair of Psychiatry, Jagiellonian University Medical College, Kraków, Poland

Aim: We aimed to systematically evaluate the prevalence and clinical characteristics of adverse events associated with the adaptogens and antidepressant drug interactions in a retrospective chart review.

Methodology: A total of 1,816 reports of adverse events were evaluated. Cases were included in the analysis if the pharmacoepidemiological analysis showed the presence of a high probability of a causal relationship between an adaptogen and antidepressant interaction and the occurrence of adverse events. The following data were extracted from the reports: age, sex, antidepressant, plant products containing adaptogens, other concomitant medications, and clinical consequences of the interactions and their possible mechanisms.

Results: Adaptogens were involved in 9% of adverse events associated with the concomitant use of antidepressants and other preparations. We identified 30 reports in which side effects presented a causal relationship with the use of antidepressants and adaptogens. Here, we present the list of adaptogens with the corresponding antidepressants and the side effects caused by their interactions: *Withania somnifera*: reboxetine (testicle pain and ejaculatory dysfunctions), sertraline (severe diarrhea), escitalopram (myalgia, epigastric pain, nausea, vomiting, restless legs syndrome, and severe cough), and paroxetine (generalized myalgia, ophthalmalgia, and ocular hypertension); *Eleutherococcus senticosus*: duloxetine (upper gastrointestinal bleeding), paroxetine (epistaxis), sertraline (vaginal hemorrhage), and agomelatine (irritability, agitation, headache, and dizziness); *Schisandra chinensis*: bupropion (arthralgia and thrombocytopenia), amitriptyline (delirium), and fluoxetine (dysuria); *Tribulus terrestris*: citalopram (generalized pruritus), escitalopram (galactorrhea), and trazodone (psoriasis relapse); *Coptis chinensis*: mianserin (arrhythmias), mirtazapine (edema of lower limbs and myalgia), and fluoxetine (gynecomastia); *Cimicifuga racemosa*: mianserin (restless legs syndrome), paroxetine (gynecomastia and mastalgia), and venlafaxine (hyponatremia); *Bacopa monnieri*: agomelatine (back pain and hyperhidrosis) and moclobemide

(myocardial infarction); *Gynostemma pentaphyllum*: duloxetine (back pain); *Cordyceps sinensis*: sertraline (upper gastrointestinal bleeding); *Lepidium meyenii*: mianserin (restless legs syndrome); and *Scutellaria baicalensis*: bupropion (seizures).

Conclusion: Clinicians should monitor the adverse events associated with the concomitant use of adaptogens and antidepressant drugs in patients with mental disorders. Aggregation of side effects and pharmacokinetic interactions (inhibition of CYP and p-glycoprotein) between those medicines may result in clinically significant adverse events.

KEYWORDS

ashwagandha, maca, jiaogulan, berberine, herb–drug interactions, depression, cytochrome, p-glycoprotein

1 Introduction

Adaptogens are defined as non-toxic substances of plant origin that are claimed to increase "non-specific" resistance to a broad spectrum of adverse biological, chemical, and physical factors, normalize body functions, and strengthen the system compromised by stress (Committee on Herbal Medicinal Products, 2008). The broad and vague definition of the term renders it of little scientific value. It is difficult to determine the minimum requirements needed for "strengthening" such a preparation. Therefore, almost every plant preparation, with which some positive effects have been indicated, can be called an adaptogen. As the principle of an adaptogenic action needs further clarification, this term is not accepted in clinical and pharmacological terminologies in the European Union and has been considered not appropriate for marketing authorization (Committee on Herbal Medicinal Products, 2008). Nevertheless, in this article, we have decided to use the term "adaptogen," as we believe it would make it easier for physicians and patients to find the results of our study. In the literature, more than 100 plants have been described as having "adaptogenic properties" (Panossian et al., 2021), of which the most extensively studied are *Withania somnifera* (ashwagandha), *Schisandra chinensis*, *Rhodiola rosea*, and *Eleutherococcus senticosus* (Panossian, 2013; Todorova et al., 2021). As the adaptogens are obtainable without prescriptions, their use has become increasingly popular. For example, according to the National Institutes of Health Office of Dietary Supplements, there are currently more than 1,300 products containing *Withania somnifera* in the United States markets alone (Speers et al., 2021), and by 2019, preparations derived from this plant had become the fifth most popular dietary supplement (Smith et al., 2020). An increasing number of studies suggest that adaptogens may alleviate fatigue, insomnia, anxiety, memory impairments, and depressive symptoms and reduce the level of perceived stress (Panossian and Wikman, 2009a; Panossian, 2013; Panossian et al., 2021; Todorova et al., 2021). Thus, these substances are commonly used by patients suffering from mental disorders, who take them along with their medication, as a form of complementary treatment or with the aim to ameliorate side effects experienced during psychopharmacotherapy. Although adaptogens are non-toxic and generally well tolerated, they still may induce adverse interactions with other drugs. Notably, plant preparations usually consist of numerous, separate, pharmacologically active substances that function as independent drugs. For instance, more than 40 withanolides, approximately 12 alkaloids, and several sitoindosides have been isolated from *Withania somnifera* (Mirjalili et al., 2009). Such a large group of bioactive compounds may significantly increase the risk of adverse events (Woroń and Siwek, 2018).

Patients treated for mental disorders are already exposed to the side effects associated with the use of polytherapy, which is defined as the use of at least two drugs at the same time. Approximately one-third of the patients in the United States are treated with at least three psychotropic medications, and this proportion has been shown to be increasing over time (Mojtabai and Olfson, 2010). Even the use of two drugs at the same time poses the risk of adverse interactions, and if seven drugs are taken simultaneously, the occurrence of such interactions is certain (Vickers et al., 2006; McIntyre et al., 2016; Schatzberg and Nemeroff, 2017; Woroń and Siwek, 2018). One of the most frequently used psychotropic drugs are antidepressants (Brody and Gu, 2015). Apart from major depressive disorder, these medicines are used to treat anxiety disorders, insomnia, eating disorders, or chronic pain. As adaptogens are suggested to alleviate the symptoms that occur in those conditions, the concomitant use of those preparations and antidepressants may be a common phenomenon. Despite the high popularity of adaptogens and the frequent use of antidepressants, adverse interactions between those two groups of substances have not been extensively studied. While the use of adaptogens in combination with other drugs is considered to be low risk, the data supporting those claims come from animal/*in vitro* studies and from the research conducted on a small group of patients that did not implement methodology specifically addressing this issue (Tandon and Yadav, 2020; Fuladi et al., 2021). As the adaptogens are registered as dietary supplements, their interactions with other drugs are not rigorously monitored by the United States Food and Drug Administration. Thus, there is an urgent need to systematically evaluate the risks associated with the use of those preparations during psychopharmacotherapy.

The aim of this research is to systematically evaluate the characteristics and incidence of adverse events associated with the concomitant use of adaptogens and antidepressant drugs in a retrospective chart review.

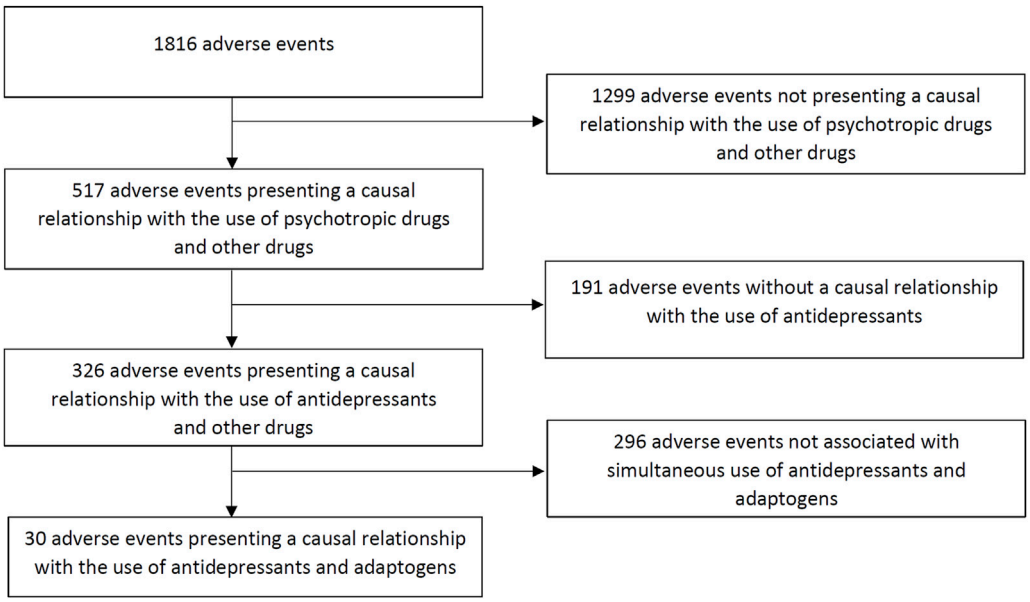

FIGURE 1
Flow chart of the retrospective chart review.

2 Materials and methods

In order to evaluate the prevalence and clinical characteristics of adverse events associated with the concomitant use of adaptogens and antidepressants, we performed a retrospective chart review according to the methodology of our previous studies on psychotropic drug interactions (Woroń and Siwek, 2018; Woroń et al., 2019; Siwek et al., 2020). All authors performed the analysis. The dataset consisted of reports on the occurrence of adverse reactions caused by the interactions between simultaneously used drugs. The reports were analyzed at the University Center for Monitoring and Research on Adverse Drug Effects, Department of Clinical Pharmacology, Jagiellonian University Medical College, Cracow. This unit has been authorized by Polish legal acts to formally monitor and report adverse events related to pharmacotherapy, as well as to provide pharmacological consultations for clinics and hospitals in the Silesian, Subcarpathian, Lesser Poland, and Holy Cross regions. Due to the increasing number of reported side events associated with the use of psychotropic drugs, this unit cooperates with the Department of Affective Disorders of Jagiellonian University Medical College. Approximately 850–1,100 consultations are made per year (Woroń et al., 2022).

In the current study, we have evaluated reports that were received from all over Poland in the period between January 2021 and November 2022. The analyzed period was selected on the basis of the availability of the data. The first reports of side effects related to the use of adaptogens were found in January 2021. The cases were included in the study when the following criteria were met: 1) patients used at least one antidepressant drug, 2) patients received at least one adaptogen, and 3) the presence of a high probability of a causal relationship in terms of pharmacodynamic interactions, pharmacokinetic interactions, or the interactions associated with the aggregation of side effects caused by the concomitant use of adaptogens and antidepressant drugs indicated by the pharmacoepidemiological analysis. The cause-and-effect relationship was indicated when the following two conditions were met: 1) the mechanism of interactions leading to the described adverse events may be demonstrated on the basis of the existing literature; 2) the discontinuation of products containing adaptogenic plant extracts resulted in the amelioration of the described side effects.

Figure 1 shows a flow chart of our retrospective chart review. We evaluated 1,816 registered adverse events, of which 517 presented a causal relationship with the use of psychotropic medication. A total of 326 adverse events were associated with the use of antidepressants, of which 30 were caused by the simultaneous use of medical products containing adaptogens (9%).

3 Results

Table 1 summarizes the data extracted from 30 adverse events causally related to the simultaneous use of adaptogens and antidepressant drugs. The mean age of the patients described in the reports was 57 ± 14.3 years. The reports included 17 women and 13 men. The group of antidepressants that showed the highest rates of adverse events was serotonin reuptake inhibitors (SSRIs, 14 patients, 46%), which involved escitalopram (five patients, 17%), sertraline (three patients, 10%), paroxetine (three patients, 10%), fluoxetine (two patients, 7%), and citalopram (one patient, 3%). Three cases (10%) demonstrated adverse events associated with the use of serotonin and norepinephrine reuptake inhibitors (SNRIs), particularly two patients (7%) treated with duloxetine and one patient (3%) with venlafaxine. Other antidepressants presenting adverse interactions with adaptogens were as follows:

TABLE 1 Interactions between adaptogens and antidepressant drugs in the analyzed group and possible interaction mechanisms. p-gp, p-glycoprotein.

Plant products containing adaptogens	Antidepressant medication	Sex/ age	Other concomitant medications	Clinical consequences of the interaction	Possible interaction mechanism
Withania somnifera	Reboxetine	M/56	Perindopril, amlodipine, and metformin	Testicle pain, ejaculatory dysfunctions, and pain during ejaculation	Pharmacokinetic: inhibition of CYP3A4 and CYP2D6 by *Withania somnifera* increased concentration and side effects of reboxetine (metabolized by CYP2D6 and CYP3A4)
	Sertraline	M/36	Doxylamine	Severe diarrhea requiring hospitalization	Addition of side effects: *Withania somnifera* may induce gastrointestinal symptoms, including diarrhea; 20% of patients treated with sertraline present diarrhea
					Pharmacokinetic: Inhibition of p-gp by *Withania somnifera* increased concentration and side effects of sertraline which is a p-gp substrate
	Escitalopram	M/58	Dapagliflozin, metformin, and zofenopril	Myalgia NRS>5	Pharmacokinetic: Inhibition of p-gp, CYP3A4, and CYP2D6 by *Withania somnifera* increased concentration and side effects of escitalopram (transported by p-gp and metabolized by CYP2D6 and CYP3A4)
	Escitalopram	F/64	Atorvastatin, metformin, perindopril, and indapamide	Epigastric pain, nausea, and vomiting	Addition of side effects: *Withania somnifera* may induce gastrointestinal symptoms including epigastric pain and nausea. The aforementioned symptoms are common side effects observed during escitalopram therapy
					Pharmacokinetic: Inhibition of p-gp, CYP3A4, and CYP2D6 by *Withania somnifera* increased concentration and side effects of escitalopram (transported by p-gp and metabolized by CYP2D6 and CYP3A4)
	Escitalopram	F/71	Formoterol, fluticasone, zofenopril, and hydrochlorothiazide	Restless legs syndrome	Pharmacokinetic: Inhibition of p-gp, CYP3A4, and CYP2D6 by *Withania somnifera* increased concentration and side effects of escitalopram (transported by p-gp and metabolized by CYP2D6 and CYP3A4)
	Escitalopram	F/58	Sitagliptin, metformin, atorvastatin, ezetimibe, and trazodone (50 mg/day)	Severe non-productive cough resistant to antitussive medication	Pharmacokinetic: Inhibition of p-gp, CYP3A4, and CYP2D6 by *Withania somnifera* increased concentration and side effects of escitalopram (transported by p-gp and metabolized by CYP2D6 and CYP3A4)
					Addition of side effects: *Withania somnifera* may induce cough which is one of the side effects observed during escitalopram therapy
	Paroxetine	F/31	Lorazepam	Generalized myalgia (NRS = 4–5), ophthalmalgia, and ocular hypertension	Pharmacokinetic: Inhibition of p-gp, CYP3A4, and CYP2D6 by *Withania somnifera* increased concentration and side effects of paroxetine (transported by p-gp and metabolized by CYP2D6 and CYP3A4)

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TABLE 1 (*Continued*) Interactions between adaptogens and antidepressant drugs in the analyzed group and possible interaction mechanisms. p-gp, p-glycoprotein.

Plant products containing adaptogens	Antidepressant medication	Sex/ age	Other concomitant medications	Clinical consequences of the interaction	Possible interaction mechanism
Eleutherococcus senticosus	Duloxetine	F/68	Bisoprolol, aspirin, clopidogrel, zofenopril, and tamsulosin	Upper gastrointestinal bleeding	Addition of side effects: *Eleutherococcus senticosus*, due to its significant antiplatelet activity, may increase the risk of bleeding in the case of concomitant use of anticoagulant and antiplatelet drugs as well as SNRI
	Paroxetine	M/64	Ticagrelor, aspirin, perindopril, allopurinol, atorvastatin, and pantoprazole	Epistaxis	Addition of side effects: *Eleutherococcus senticosus*, due to its significant antiplatelet activity, may increase the risk of bleeding in the case of the concomitant use of anticoagulant and antiplatelet drugs as well as SSRI
					Pharmacokinetic: Inhibition of p-gp by *Eleutherococcus senticosus* increased the concentration and side effects of paroxetine which is a p-gp substrate
	Sertraline	F/41	Bisoprolol, rivaroxaban, propafenone, and pantoprazole	Vaginal hemorrhage	Addition of side effects: *Eleutherococcus senticosus*, due to its significant antiplatelet activity, may increase the risk of bleeding in the case of the concomitant use of anticoagulant and antiplatelet drugs as well as SSRI
					Pharmacokinetic: Inhibition of p-gp by *Eleutherococcus senticosus* increased the concentration and side effects of sertraline which is a p-gp substrate
	Agomelatine	F/39	Alprazolam and ethinyloestradiol + dienogest	Irritability, agitation, headache, and dizziness	Pharmacokinetic: *Eleutherococcus senticosus* inhibits p-gp, CYP2C9, and CYP1A2, increasing the concentration and side effects of agomelatine (transported by p-gp and metabolized by CYP2C9 and CYP1A2)
					Addition of side effects: Irritability and headache have been listed as some of the side effects observed during the use of *Eleutherococcus senticosus* as well as agomelatine
Tribulus terrestris	Citalopram	M/29	Lorazepam	Generalized pruritus	Pharmacokinetic: *Tribulus terrestris* inhibits CYP3A4, increasing the concentration and side effects of citalopram (metabolized by CYP3A4)
	Escitalopram	F/31	Zolpidem	Galactorrhea	Pharmacokinetic: *Tribulus terrestris* inhibits CYP3A4, increasing the concentration and side effects of escitalopram (metabolized by CYP3A4)
	Trazodone	M/39	Ramipril, indapamide, and metoprolol	Psoriasis relapse	Pharmacokinetic: *Tribulus terrestris* inhibits CYP3A4, increasing the concentration and side effects of trazodone (metabolized by CYP3A4). By this interaction, *Tribulus terrestris* may increase the risk of psoriasis relapse. This is of clinical significance if trazodone is used in daily doses above 300 mg when it reveals significant SSRI activity

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TABLE 1 (*Continued*) Interactions between adaptogens and antidepressant drugs in the analyzed group and possible interaction mechanisms. p-gp, p-glycoprotein.

Plant products containing adaptogens	Antidepressant medication	Sex/ age	Other concomitant medications	Clinical consequences of the interaction	Possible interaction mechanism
Schisandra chinensis	Bupropion	M/42	Alprazolam	Generalized arthralgia	Pharmacokinetic: *Schisandra chinensis* inhibits CYP2B6, CYP2C9, CYP3A4, and CYP2E1, increasing the concentration and side effects of bupropion (metabolized by CYP2B6, CYP2C9, CYP3A4, and CYP2E1)
	Bupropion	M/40	Hydroxyzine	Thrombocytopenia	Pharmacokinetic: *Schisandra chinensis* inhibits CYP2B6, CYP2C9, CYP3A4, and CYP2E1, increasing the concentration and side effects of bupropion (metabolized by CYP2B6, CYP2C9, CYP3A4, and CYP2E1)
	Amitriptyline	F/79	Metoprolol, ramipril, torsemide, potassium, etoricoxib, and glucosamine sulfate	Delirium	Pharmacokinetic: *Schisandra chinensis* inhibits CYP3A4, CYP2C19, and CYP2C9, increasing the concentration and side effects of amitriptyline (metabolized by CYP3A4, CYP2C19, and CYP2C9)
	Fluoxetine	F/74	Perindopril, amlodipine, furosemide, and chondroitin sulfate	Dysuria	Pharmacokinetic: *Schisandra chinensis* inhibits CYP2C9, increasing the concentration and side effects of fluoxetine (metabolized by CYP2C9)
Gynostema pentaphyllum	Duloxetine	M/44	Melatonin	Lower back pain (NRS = 5–6) with increased muscular tension	Pharmacokinetic: *Gynostema pentaphyllum* inhibits CYP2D6, increasing the concentration and side effects of duloxetine (metabolized by CYP2D6)
Cordyceps sinensis	Sertraline	M/58	Ticagrelor, aspirin, ramipril, pitavastatin, bisoprolol, and dexlansoprazole	Upper gastrointestinal bleeding	Addition of side effects: *Cordyceps sinensis*, due to its significant antiplatelet activity, may increase the risk of bleeding in the case of concomitant use of anticoagulant and antiplatelet drugs as well as SSRIs
Cimicifuga racemosa	Mianserin	F/56	Bisoprolol	Restless legs syndrome	Pharmacokinetic: *Cimicifuga racemosa* inhibits CYP2D6 and CYP3A4, increasing the concentration and side effects of mianserin (metabolized by CYP2D6 and CYP3A4)
	Paroxetine	F/61	Lornoxicam and glucosamine sulfate	Gynecomastia and mastalgia (NRS>5)	Pharmacokinetic: *C. racemosa* inhibits CYP2D6, increasing the concentration and side effects of paroxetine (metabolized by CYP2D6)
					Addition of side effects: Breast pain/enlargement has also been observed during the use of *Cimcifuga racemosa* extracts
	Venlafaxine	F/58	Alprazolam, zofenopril, and lercanidipine	Hyponatremia	Pharmacokinetic: *Cimicifuga racemosa* inhibits CYP2D6 and CYP3A4, increasing the concentration and side effects of venlafaxine (metabolized by CYP2D6 and CYP3A4)
Coptis chinensis	Mianserin	M/60	Tamsulosin, budesonide, fluticasone, and theophylline	Ventricular arrhythmias	Pharmacokinetic: *Coptis chinensis* inhibits CYP2D6 and CYP3A4à increasing concentration and side effects of mianserin (metabolized by CYP2D6 and CYP3A4)
	Mirtazapine	F/48	Oxazepam and bilastine	Edema of lower limbs and myalgia	Pharmacokinetic: *Coptis chinensis* inhibits CYP3A4, increasing the concentration and side effects of mirtazapine (metabolized by CYP3A4)

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TABLE 1 (*Continued*) **Interactions between adaptogens and antidepressant drugs in the analyzed group and possible interaction mechanisms. p-gp, p-glycoprotein.**

Plant products containing adaptogens	Antidepressant medication	Sex/age	Other concomitant medications	Clinical consequences of the interaction	Possible interaction mechanism
Scutellaria baicalensis	Fluoxetine	F/32	Alprazolam	Gynecomastia	Pharmacokinetic: *Coptis chinensis* inhibits CYP3A4, increasing the concentration and side effects of fluoxetine (metabolized by CYP3A4)
	Mianserin	M/64	Doxazosin, perindopril, and indapamide	Restless legs syndrome	Pharmacokinetic: *Lepidium meyenii* inhibits CYP3A4, increasing the concentration and side effects of mianserine (metabolized by CYP3A4)
	Bupropion	F/67	Chondroitin sulfate, tramadol, sertraline, and etoricoxib	Seizures	Pharmacokinetic and addition of side effects: *Scutellaria baicalensis* strongly inhibits CYP2C9, increasing the concentration and side effects of bupropion (metabolized by CYP2C9). As tramadol, sertraline, and bupropion decrease the seizure threshold, increased concentration of the latter one leads to more severe outcomes of the addition of side effects
Bacopa monnieri	Agomelatine	F/42	Sitagliptin, metformin, and bisoprolol	Back pain and hyperhidrosis	Pharmacokinetic: *Bacopa monnieri* inhibits p-gp, CYP1A2, CYP2C9, and CYP2C19, increasing the concentration and side effects of agomelatine (transported by p-gp, and metabolized by CYP1A2, CYP2C9, and CYP2C19)
	Moclobemide	M/39	Doxylamine, metformin, dapagliflozin, and rosuvastatin	Myocardial infarction	Pharmacokinetic: *Bacopa monnieri* inhibits CYP2C19, increasing the concentration and side effects of moclobemide (metabolized by CYP2C19)

reboxetine (one patient, 3%), bupropion (three patients, 10%), trazodone (one patient, 3%), mianserin (three patients, 10%), mirtazapine (one patient, 3%), amitriptyline (one patient, 3%), agomelatine (two patients, 7%), and moclobemide (one patient, 3%). In the case of adaptogens, interactions involved *Withania somnifera* (seven patients, 23%), *Eleutherococcus senticosus* (four patients, 13%), *Schisandra chinensis* (four patients, 13%), *Tribulus terrestris* (three patients), *Coptis chinensis* (three patients, 10%), *Cimcifuga racemosa* (three patients, 10%), *Bacopa monnieri* (two patients, 7%), *Gynostema pentaphyllum* (one patient, 3%), *Cordyceps sinensis* (one patient, 3%), *Lepidium meyenii* (one patient, 3%), and *Scutellaria baicalensis* (one patient, 3%). Most of the analyzed adverse events resulted from pharmacokinetic interactions (20 reports, 67%). In the case of two patients (7%), they were caused by the addition of side effects. Eight adverse events were of mixed origin (27%, the presence of both pharmacokinetic interactions and the addition of side effects). A detailed description of the proposed mechanisms and their clinical consequences are shown in Table 1.

According to the reports, the discontinuation of products containing adaptogenic plant extracts led to the amelioration of the described symptoms. Corrective therapy was required for severe adverse reactions. In all the described cases, a causal relationship was established between the combination of the drug and the product containing plant extracts and the side effects that the patient experienced.

4 Discussion

To the best of our knowledge, this is the first retrospective chart review evaluating the prevalence and clinical characteristics of the adverse events associated with the concomitant use of adaptogens and antidepressant drugs. A thorough evaluation of 326 reports showed that 9% of adverse events caused by interactions of antidepressants with other drugs were most likely caused by their concomitant use with adaptogens, particularly *Withania somnifera*, *Eleutherococcus senticosus*, *Schisandra chinensis, Tribulus terrestris*, *Coptis chinensis*, *Cimcifuga racemosa*, *Bacopa monnieri*, *Gynostema pentaphyllum*, *Cordyceps sinensis*, *Lepidium meyenii*, and *Scutellaria baicalensis.* Notably, in all of the cases, discontinuation of the adaptogenic preparations led to remission of the described symptoms. Table 2 shows the side effects associated with the use of those adaptogens and their effects on cytochrome P450 and p-glycoprotein. Table 3 presents the relationships between antidepressants drugs and cytochrome isoenzymes and p-glycoprotein.

Withania somnifera was associated with the highest number of adverse events caused by the simultaneous use of antidepressants and adaptogens, presumably because it is one of the most commonly used dietary supplements (Smith et al., 2020). Interactions were mainly associated with the use of SSRIs. Proposed mechanisms underlying those events involve: 1) interactions between adaptogen and cytochrome 450 isoenzymes responsible for antidepressant metabolism and 2) the addition of side effects of both substances. The first mechanism is related to the suggested inhibitory effect of *Withania somnifera* extracts on CYP3A4 and CYP2D6

TABLE 2 Side effects and possible interaction mechanisms of the analyzed adaptogens. ↑ indicating induction and ↓ indicating inhibition.

	Side effect	Interactions with cytochrome	Interactions with p-glycoprotein
Withania somnifera	Somnolence, epigastric pain/discomfort, diarrhea, giddiness, drowsiness, hallucinations, vertigo, rhinitis, cough, cold, decreased appetite, nausea, constipation, dry mouth, hyperactivity, nocturnal cramps, blurring of vision, hyperacidity, skin rash, and weight gain (Tandon and Yadav, 2020)	↑ ↓/none CYP3A4	↓ (Hassan et al., 2021)
		↓/none CYP2D6	
		↓ CYP2B6	
		↑ CYP1A2	
		(Brinker (2010); Savai et al. (2013); Savai et al. (2015); Sultana and Sultan (2018); Kumar et al. (2021b); Haron et al. (2022))	
Eleutherococcus senticosus	Insomnia, shifts in heart rhythm, tachycardia, extrasystoles, palpitations, headache, pericardial pain, elevated blood pressure, irritability, melancholy, anxiety, and bleeding (European Medicine's Agency, 2008)	↓ CYP2C9	↓ (Takahashi et al., 2010)
		↓ CYP2E1	
		(Guo et al., 2014)	
Schisandra chinensis	Dyspepsia, anorexia, urticaria, restlessness, insomnia, and dyspnea (Bove et al., 2010; St. John, 2018)	↓ CYP3A4	↓ (F. Zhang et al., 2022)
		↓ CYP2B6	
		↓ CYP2C8	
		↓ CYP2C9	
		↓ CYP2C19	
		↓ CYP2E1	
		(Jiang et al., 2010; Seo et al., 2021b)	
Tribulus terrestris	Abdominal pain/distension/discomfort, diarrhea, gastric upset, halitosis, headache, insomnia, irritability, nausea, and priapism (Gama et al., 2014; Campanelli et al., 2016)	↓ CYP3A4	—
		(Wang et al., 2022)	
Coptis chinensis	—	↓ CYP3A4	↑ (Yu et al., 2018)
		↓ CYP2C9	
		↓ CYP2D6	
		(Guo et al., 2012; Yu et al., 2018)	
Cimcifuga racemosa	Stiffening of extremities, gastric pain, allergic reactions, gastrointestinal symptoms (dyspeptic disorders and diarrhea), facial edema, and peripheral edema (EMA, 2017)	↓ CYP3A4,	Not significant (Gurley et al., 2006)
		↓ CYP2D6	
		(J. Li et al., 2011; Tsukamoto et al., 2005)	

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TABLE 2 (*Continued*) Side effects and possible interaction mechanisms of the analyzed adaptogens. ↑ indicating induction and ↓ indicating inhibition.

	Side effect	Interactions with cytochrome	Interactions with p-glycoprotein
Bacopa monnieri	Gastrointestinal symptoms (increased stool frequency, nausea, and abdominal cramps) (Walker and Pellegrini, 2023)	↓ CYP2C9	↓ (Singh et al., 2013)
		↓ CYP2C19	
		↓ CYP1A2	
		↓ CYP2D6	
		↓ CYP3A4	
		(Ramasamy et al., 2014)	
Gynostema pentaphyllum	Nausea and increased bowel movements (Chen and Su, 1989)	↓ CYP2D6	↓ (Zhu et al., 2012)
		↓ CYP2C8	
		↓ CYP3A4	
		↓ CYP2C9	
		(He et al., 2013)	
Cordyceps sinensis	Bleeding, dry mouth, abdominal distension, throat discomfort, and headache (Hatton et al., 2018; X. Yu et al., 2019)	—	—
Lepidium meyenii	—	↓/none CYP3A4	—
		(Brinker, 2010; Ibrahim et al., 2022; Y. Zhang et al., 2019)	
Scutellaria baicalensis	Skin allergy, platelet count reduction, pneumonia, and liver damage (Kiguchi et al., 2000; Takeshita et al., 2001; Dhanasekaran et al., 2013; Lin et al., 2016)	↓ CYP2C9	↓ (Miao et al., 2016)
		↑ CYP2E1	
		↓ CYP2C19	
		↓CYP4F2	
		↓/↑ CYP3A4	
		↓/↑ CYP2B6	
		↓ CYP1A2	
		(Zhou et al., 2021)	

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TABLE 3 Antidepressants as substrates of cytochrome P450 (CYP450) and p-glycoprotein (p-gp). X–effects shown in animal and human studies; ((X))—effect shown in animal studies but is not confirmed in human and human cell studies; X!—strong effect; X?—effect demonstrated in animal studies, but no clinical trials or studies on human cells have been conducted so far (Siwek, 2023).

	CYP450 substrate	P-gp substrate
Agomelatine	1A2 > 2C19/2C9	X
Amitriptyline	2D6/3A4/2C19	((X))
	>1A2/2C9/2B6/2C8	
Bupropion	2B6 > 2E1	—
Citalopram	2C19 > 3A4/2D6	X
Duloxetine	1A2/2D6 >2C9	—
Escitalopram	2C19 >3A4/2D6	X
Fluoxetine	2D6 >3A4/3A5,	((X))
	/2C9/2C19, 2B6/1A2	
Mirtazapine	3A4 >2D6/1A2	
Moclobemide	2C19> 2D6	
Paroxetine	2D6 >3A4/1A2/2C19	X
Reboxetine	3A4 > 2D6	—
Sertraline	2C19 > 2C9, 3A4	X!
Trazodone	3A4 > 2D6, 1A2	X
Venlafaxine	2D6 > 3A4	—
Mianserin	2D6 > 3A4	—

(Brinker, 2010; Sultana and Sultan, 2018). This results in an increase in the concentration and side effects of antidepressants metabolized by those cytochromes, particularly escitalopram (myalgia of intensity >5 according to the numeric rating scale (NRS), epigastric pain, nausea, vomiting, restless legs syndrome, and severe non-productive cough), paroxetine (generalized myalgia (NRS = 4–5), ophthalmalgia, and ocular hypertension), and reboxetine (testicle pain, ejaculatory dysfunctions, and pain during ejaculation). The addition of the side effects was involved in the occurrence of severe diarrhea requiring hospitalization in a patient treated with sertraline and with the presence of epigastric pain, nausea, and vomiting in the case of an individual treated with escitalopram. Those two drugs are one of the least tolerated antidepressants in terms of gastrointestinal side effects (Oliva et al., 2021). For example, diarrhea was presented in up to 20% of patients receiving sertraline (Sertraline Side Effects, 2023). Loose stools and epigastric pain were also reported as one of the most common side effects (>5%) among individuals receiving *Withania somnifera* (Tandon and Yadav, 2020). Therefore, the overlap of those symptoms caused by the use of *Withania somnifera*, sertraline, and escitalopram are plausible explanations for observed adverse events. To the best of our knowledge, there are no studies on herb–drug interactions between this adaptogen and antidepressant drugs. One *in vitro* study suggests that *Withania somnifera* extracts have the potential to cause clinically significant herb–drug interactions through their associations with CYP3A4 and CYP2B6 metabolism pathways (Kumar et al., 2021a). However, there are conflicting results concerning the nature of those interactions. *In vitro* studies reported that *Withania somnifera* extracts may inhibit (Sultana and Sultan, 2018), induce (Kumar et al., 2021a), or reveal no significant impact on CYP3A4 (Savai et al., 2013, Savai et al., 2015). Further studies are required to understand the associations between CYP isoenzymes and *Withania somnifera* extracts, as well as the clinical relevance of these findings.

Eleutherococcus senticosus is a commonly used adaptogen that is suggested to increase the mental performance of patients with mild fatigue and weakness (A. Panossian and Wikman, 2009b). We identified three cases of adverse bleeding-related events (vaginal hemorrhage, epistaxis, and upper gastrointestinal bleeding) associated with the use of this adaptogen with SSRIs (paroxetine and sertraline) and an SNRI (duloxetine). Possible mechanisms underlying those interactions include the addition of side effects. Studies showed that *Eleutherococcus senticosus* contains dihydroxybenzoic acid, which has antiplatelet activity (Yun-choi et al., 1987; Friedman et al., 2007) and may increase the risk of hemorrhage associated with the use of SSRIs and SNRIs (Zeiss et al., 2021). There is only one study reporting adverse bleeding-related events associated with the use of this adaptogen. Friedman et al. (2007) reported a case of multifocal and recurrent spontaneous subarachnoid hemorrhage caused by the use of *Eleutherococcus senticosus* in combination with other herbal supplements (red clover and dong quai) (Friedman et al., 2007). Cases of adverse bleeding-related events associated with the use of those preparations should be reported in the literature, and herbal medicines should be considered the possible cause of hemorrhage (Friedman et al., 2007). We have also shown a case of the patient presenting increased irritability, agitation, headache, and dizziness when agomelatine was simultaneously used with *Eleutherococcus senticosus*. We hypothesize that this adverse event may be associated with the inhibitory effect of this adaptogen on CYP2C9 and CYP1A2 (Brinker, 2010; Guo et al., 2014), leading to the increased concentration and side effects of agomelatine (Carvalho et al., 2016). Furthermore, irritability and headache have been listed as the side effects associated with the use of *Eleutherococcus senticosus*, indicating the presence of the addition of side effects.

Tribulus terrestris is commercialized with indications to improve sexual and athletic performance (Stefanescu et al., 2020). It has been shown that extracts obtained from this plant exhibit inhibitory effects on CYP3A4 (Wang et al., 2022). We have identified three reports of adverse events associated with the concomitant use of this adaptogen and the antidepressants metabolized by this enzyme. Inhibition of CYP3A4 by *Tribulus terrestris* preparations was most likely associated with the increase in the concentration and the severity of side effects of citalopram (generalized pruritus (Citalopram Side Effects, 2023)), escitalopram (galactorrhea (Ravi et al., 2014)), and trazodone (psoriasis relapse (Barth and Baker, 1986)). To the best of our knowledge, there are no studies reporting herb–drug interactions associated with the use of this herb. Our results show that attention should be paid when *Tribulus terrestris* is used with drugs metabolized by CYP3A4.

Schisandra chinensis is widely used to treat fatigue and insomnia (Sowndhararajan et al., 2018). The major bioactive substances in these preparations are lignans. This pharmacologically heterogeneous group contains more than 40 particles, of which

the most commonly evaluated are: schisandrin, schisandrin A, schisandrin C, deoxyschisandrin, shisanthenol, schisantherin A, gomisins (A, B, C, and N), and wuweizisu C (Sowndhararajan et al., 2018; Seo et al., 2021a). Those substances inhibit numerous cytochrome isoenzymes, including CYP3A4, CYP2B6, CYP2C8, CYP2C9, and CYP2C19, and thus their coadministration with the drugs may result in clinically relevant pharmacokinetic interactions (detailed analysis is presented in Seo et al., 2021a). It has been shown that through the inhibition of CYP3A4, *Schisandra chinensis* extracts increase the concentrations of tacrolimus in liver transplant patients (Jiang et al., 2010) as well as midazolam in rats (Li et al., 2013). In our study, we have found four cases of adverse events related to the use of this adaptogen. We hypothesize that through the inhibition of CYP2B6, CYP2C9, CYP2C9, CYP2C19, and CYP3A4, *Schisandra chinensis* preparations increased the concentration and side effects of bupropion (thrombocytopenia (Altintas et al., 2013) and generalized arthralgia (Ornetti et al., 2004)), amitriptyline (delirium (King and Ashraf, 2018)), and fluoxetine (dysuria (Fluoxetine Side Effects, 2023)).

Cimcifuga racemosa is suggested to ameliorate menopausal symptoms such as hot flashes, profuse sweating, anxiety, and insomnia (Mahady, 2005). It has been shown that ethanolic extracts derived from this plant contain eight triterpene glycosides that inhibit CYP3A4, as well as two alkaloids (protopine and allocryptopine) that revealed inhibitory effects on CYP2D6 (J. Li et al., 2011). We have identified three cases of adverse events caused by the concomitant use of this adaptogen and antidepressants metabolized by those cytochromes. We hypothesize that the inhibition of CYP2D6 increased the concentration and side effects of venlafaxine (hyponatremia; additionally associated with the inhibition of CYP3A4), mianserin (restless legs syndrome (Hoque, 2020)), and paroxetine (gynecomastia/mastalgia (Damsa et al., 2003)). In the latter case, the addition of side effects may be involved, as breast pain/enlargement has been reported during *C. racemosa* treatment (Black Cohosh, 2003; Mahady, 2005).

Coptis chinensis was traditionally used to treat gastrointestinal symptoms and insomnia (J. Wang et al., 2019). Berberine, one of the most important active constituents of this plant, is being studied for its possible use in the treatment of mood disorders (Fan et al., 2019). Our analysis presented three cases of clinically significant drug–herb interactions associated with the use of *Coptis chinensis*. Their plausible mechanisms involve the inhibition of CYP2D6 and CYP3A4 by berberine (Guo et al., 2012), which increases the concentration and side effects of mirtazapine (edema of lower limbs and myalgia (Lai et al., 2016)), as well as inhibition of CYPD6 (Guo et al., 2012) that increases concentration and side effects of fluoxetine (gynecomastia (Boulenger et al., 2003)) and mianserin (ventricular arrhythmias (Haine et al., 2006)).

Bacopa monnieri has been traditionally used as a "brain tonic," which was intended to enhance memory and concentration (Ramasamy et al., 2014). Studies suggest that extracts derived from this plant can contribute to herb–drug interactions, as they have an inhibitory effect on the activity of many cytochrome isoenzymes such as CYP2C9, CYP2C19, CYP1A2, CYP2D6, and CYP3A4 (Ramasamy et al., 2014). Animal studies have shown that *Bacopa monnieri* extracts increase intestinal absorption and reduce first-pass metabolism of amitriptyline through the inhibition of CYP3A and CYP2C and decrease oral clearance of this drug (Khurshid et al., 2018). To the best of our knowledge, there is only one study presenting adverse events related to the drug interaction with this adaptogen. Acquarulo et al. (2022) showed the case of a 58-year-old patient with Sjogren's syndrome presenting cholinergic toxicity symptoms (hyperhidrosis, malaise, nausea, and tachycardia) associated with the concomitant use of *Bacopa monnieri* and cevimeline. It has been suggested that the mechanism involved the inhibition of cytochrome isoenzymes responsible for the metabolism of this drug (CYP3A4 and CYP2D6). Clinical improvement has been shown after discontinuation of the supplement (Acquarulo et al., 2022). In this study, we have presented two cases of side effect events associated with the use of this adaptogen and antidepressant treatment, particularly with agomelatine (back pain and hyperhidrosis) and moclobemide (myocardial infarction). *Bacopa monnieri* extracts may increase the concentration and side effects of drugs metabolized by CYP1A2 (agomelatine) and CYP2C19 (moclobemide), thus leading to the aforementioned symptoms. Since *Bacopa monnieri* has an impact on major CYP isoforms responsible for drug metabolism, physicians should be aware of the risk of herb–drug interactions associated with the use of this adaptogen.

Cordyceps sinensis is a member of the Ascomycetes fungus family, which grows on the dorsum of caterpillar larvae (*Hepialis armoricanus*). It is commonly used as a dietary supplement with the aim to enhance athletic performance, benefit the immune system, and promote longevity (Hatton et al., 2018). In this study, we have presented the case of upper gastrointestinal bleeding associated with the concomitant use of this adaptogen and sertraline. Plausible mechanisms responsible for this adverse event were the addition of side effects. A recent study has identified two polysaccharides (purified exopolysaccharides and purified intercellular exopolysaccharides) in *Cordyceps sinensis*, which showed dose-dependent inhibition of platelet activation and aggregation (Mao et al., 2022). In addition, it has been clinically observed that the daily intake of *Cordyceps sinensis* may result in prolonged bleeding after surgery (Hatton et al., 2018). Thus, physicians should be aware that the use of this adaptogen may increase the risk of hemorrhage in a group of patients treated with antidepressant drugs revealing antiplatelet effects, such as SSRIs (Laporte et al., 2017).

Lepidium meyenii (maca) is popularly referred to as a "natural drug" for the improvement of sexual desire, despite limited evidence to support those claims (Shin et al., 2010). To the best of our knowledge, there are no previous reports of preclinical or clinical drug interactions associated with the use of this adaptogen (Sprouse and Van Breemen, 2016). *In silico* analysis suggests that one of the active compounds of maca (N-(3-methoxybenzyl)-(9Z,12Z,15Z)-octadecatrienamide) may reveal CYP3A4 inhibitory potential (Ibrahim et al., 2022). Through the inhibition of this cytochrome isoenzyme, maca could lead to the increased concentration and side effects of mianserin, leading to the development of restless legs syndrome observed in the reported case in our study. However, a recent *in vitro* study has shown no significant induction or inhibition of maca extracts on CYP3A4 (Y. Zhang et al., 2019). More studies are required to evaluate the risk of herb–drug interactions associated with the use of *Lepidium meyenii* preparations.

Scutellaria baicalensis is commonly used in folk medicine to treat depressive symptoms (W. Zhu et al., 2008). Studies indicate that this plant comprises many bioactive compounds, such as baicalein, baicalin, and wogonin, which are associated with pharmacokinetic and pharmacodynamic interactions with a wide range of drugs (Zhou et al., 2021). We have shown the case of a patient who suffered an epileptic seizure as a side effect related to the simultaneous use of sertraline, tramadol, bupropion, and *Scutellaria baicalensis* preparation. Bioactives of this plant present complex interactions with cytochrome isoenzymes responsible for bupropion metabolism. Aqueous extracts of this herb strongly inhibit CYP2C9, while baicalein and luteolin may inhibit CYP2B6 (Noh et al., 2015; Cao et al., 2017; Zhou et al., 2021). As tramadol and bupropion decrease the seizure threshold, the increased concentration of the latter leads to more severe outcomes of the addition of side effects (Davidson, 1989; Boostani and Derakhshan, 2012). However, it is important to emphasize that there is a significant discrepancy between studies evaluating interactions between *Scutellaria baicalensis* active compounds and cytochrome isoenzymes, indicating their contradictory activity (induction or inhibition) (summarized in Zhou et al. (2021)). The composition of the preparation may significantly affect the metabolism of bupropion. For example, a high concentration of baicalin may significantly induce CYP2B6-catalyzed hydroxylation of this drug (Fan et al., 2009).

Gynostema pentaphyllum (jiaogulan, herb of immortality) is described as a calming adaptogen providing "longevity and optimum wellbeing." Gypenosides, one of the most pharmacologically active components of this herb, present significant inhibition of CYP2D6, which is capable of inducing herb–drug interactions. We have identified one side effect event associated with the simultaneous use of *Gynostema pentaphyllum* and an antidepressant metabolized by this cytochrome isoenzyme, which is duloxetine. We hypothesize that through CYP2D6 inhibition, gypenosides increased the concentration and side effects of duloxetine, leading to the occurrence of side effects in the form of lower back pain with increased muscular tension.

Additional mechanisms through which adaptogens interact with other drugs may involve their influence on p-glycoprotein. This protein complex is extensively expressed in the intestinal epithelium and blood–brain barrier where it is responsible for pumping xenobiotics (including drugs) out of the cells (Kim, 2002). Most of the aforementioned herbs contain active compounds which interact with p-glycoprotein. It has been shown that extracts of *Withania somnifera*, *Eleutherococcus senticosus*, *Schisandra chinensis*, *Bacopa monnieri*, *Gynostema pentaphyllum*, and *Scutellaria baicalensis* inhibit the activity of this protein complex. These substances may affect the distribution of antidepressant drugs that are p-glycoprotein substrates. Inhibition of this transport system may lead to an increase in their concentration in the central nervous system and more severe side effects. Antidepressants whose metabolism can be altered by the aforementioned mechanism include sertraline, agomelatine, citalopram, escitalopram, trazodone, and paroxetine (Kim, 2002; O'Brien et al., 2012; Elmeliegy et al., 2020).

The simultaneous use of herbal medicines and prescribed medication is a common phenomenon (Agbabiaka et al., 2018), and the application of adaptogens is becoming popular. Intriguingly, the prevalence of interactions between those preparations and antidepressant drugs was twofold higher than the occurrence of adverse events caused by the interactions of antidepressants with over-the-counter drugs (4%) that were presented in our previous study (Woroń et al., 2022). In clinical practice, the prevalence of those interactions may be much higher. Psychiatrists and physicians may not inquire about the use of adaptogens, as knowledge about the herb–drug interactions in this group of preparations is scarce. Patients may not report the intake of plant-based supplements as they do not consider them as medicines (Agbabiaka et al., 2018). Clinicians should be aware that the risk of the occurrence of herb–drug interactions may be age-related. The mean age of the patients described in the reports was 57 ± 14.3 years, which stays in line with the results of our previous studies (Woroń and Siwek, 2018; Woroń et al., 2019, 2022; Siwek et al., 2020).

There are several limitations to our study. Our study relies on the material of the reported side effects, which may underestimate the frequency of their occurrence since not all physicians provide such reports. Additionally, our analysis covers a relatively narrow time range. The analyzed period was selected on the basis of the availability of the data. The first reports of side effects related to the use of adaptogens were found in January 2021. Since then, the increasing popularity of these preparations has been observed, which translated into an increasing number of adverse events.

5 Conclusion and recommendations

- Clinicians should evaluate the presence of overlap between cytochrome P450 isoenzymes involved in the metabolism of adaptogens and antidepressant drugs used by the patients to counteract the occurrence of pharmacokinetic interactions.
- Adaptogen–drug interactions may lead to life-threatening side effects, e.g., upper gastrointestinal bleeding or myocardial infarction as presented in our study.
- Physicians, psychiatrists, and pharmacists should ask patients about the usage of adaptogens and inform them about the risks associated with the concomitant use of those preparations with antidepressants.
- The use of adaptogens should be documented in the patient's medical records, and the occurrence of herb–drug interactions associated with the use of those preparations should be reported.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Materials, further inquiries can be directed to the corresponding author.

Author contributions

MS: conceptualization, data curation, formal analysis, investigation, methodology, supervision, and writing–review and editing. JW: conceptualization, data curation, formal analysis, investigation, methodology, supervision, and writing–review and

editing. AW: formal Analysis, investigation, and writing–review and editing. JG: formal analysis, investigation, and writing–review and editing. AC: conceptualization, formal analysis, investigation, methodology, writing–original draft, and writing–review and editing.

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Conflict of interest

Author JG was employed by the Pharmacotherapy Safety Team.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The authors declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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EDITED BY
Anna Tabęcka-Łonczynska,
University of Information Technology and Management in Rzeszow, Poland

REVIEWED BY
Pritesh Jain,
University of California, San Diego, United States
Wladyslaw Lason,
Polish Academy of Sciences, Poland

*CORRESPONDENCE
Yunfeng Zhou
✉ zyf@henu.edu.cn
Xinmei Xie
✉ xxm@vip.henu.edu.cn
Xiaobin Pang
✉ pxb@vip.henu.edu.cn

†These authors have contributed equally to this work and share first authorship

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Targeting mitophagy for depression amelioration: a novel therapeutic strategy

Wangjun Xu[1†], Weiping Gao[1†], Yukun Guo[1], Feng Xue[1], Lulu Di[1], Shaojie Fang[1], Linlin Fan[2], Yangyang He[1,3], Yunfeng Zhou[1,4*], Xinmei Xie[1,4*] and Xiaobin Pang[1,3,4*]

[1]School of Pharmacy, Henan University, Kaifeng, China, [2]Henan Key Laboratory of Brain Targeted Bio-nanomedicine, School of Pharmacy, Henan University, Kaifeng, China, [3]Institutes of Traditional Chinese Medicine, Henan University, Kaifeng, China, [4]Henan Province Engineering Research Center of High Value Utilization to Natural Medical Resource in Yellow River Basin, School of Pharmacy, Henan University, Kaifeng, China

Major depressive disorder is a global psychiatric condition characterized by persistent low mood and anhedonia, which seriously jeopardizes the physical and mental well-being of affected individuals. While various hypotheses have been proposed to explicate the etiology of depression, the precise pathogenesis and effective treatment of this disorder remain elusive. Mitochondria, as the primary organelles responsible for cellular energy production, possess the ability to meet the essential energy demands of the brain. Research indicated that the accumulation of damaged mitochondria is associated with the onset of depression. Mitophagy, a type of cellular autophagy, specifically targets and removes excess or damaged mitochondria. Emerging evidence demonstrated that mitophagy dysfunction was involved in the progression of depression, and several pharmacological interventions that stimulating mitophagy exerted excellent antidepressant actions. We provided an overview of updated advancements on the regulatory mechanism of mitophagy and the mitophagy abnormality in depressed patients and animals, as well as in cell models of depression. Meanwhile, various therapeutic strategies to restore mitophagy for depression alleviation were also discussed in this review.

KEYWORDS

depression, mitophagy, mitochondria, drug therapy, regulatory mechanism

1. Introduction

Major depressive disorder (MDD) is a multifactorial psychiatric disorder characterized by persistent feelings of sadness and linked with deleterious effects on cognitive, affective, and physical well-being. Approximately 264 million individuals across the globe, accounting for about 4.5% of the global population, are afflicted with depression (Disease et al., 2018). Furthermore, the global incidence of depression has risen by 28% due to the impact of the COVID-19 pandemic (Collaborators, 2021). The lifetime prevalence of depression fluctuates between 15 and 18%, implying that nearly one in every five persons will undergo an episode at some juncture in their lives (Bromet et al., 2011). Researchers have extensively explored the etiology of depression and put forth diverse hypotheses, encompassing monoamine, neuroendocrine, neurotrophic factors, epigenetic, inflammatory, and hypothalamic–pituitary–adrenal axis hypotheses, etc., (Kim, 2016; Keller et al., 2017; Allen et al., 2018; Zhang G. et al.,

2020). However, a definitive theory that comprehensively explicates its pathological mechanism remains elusive. The current first-line antidepressants are predominantly based on the monoamine hypothesis (McCarron et al., 2021). Despite their effectiveness, these medications may take up to 6 weeks to manifest therapeutic effects and frequently give rise to adverse reactions such as headaches, gastrointestinal symptoms, sexual dysfunction, and agitation (Marwaha et al., 2023). Furthermore, approximately one-third to half of depressed patients do not respond to multiple antidepressants (Rush et al., 2009; Cipriani et al., 2018). The two leading diagnostic systems for MDD, namely the Diagnostic and Statistical Manual of Mental Disorders and the International Classification of Diseases, are extensively employed in hospital, outpatient, and community settings (First, 2013; The Lance, 2019). However, these diagnoses should be ascribed only after a single bout of depression lasting for a minimum of 2 weeks, and following the exclusion of other psychiatric diagnoses like anxiety, schizophrenia, and bipolar disorder to ensure that symptoms are exclusively attributed to depression (Malhi and Mann, 2018). Consequently, delving into the etiology of depression from novel perspectives is crucial for guiding clinical diagnosis and facilitate the development of therapeutic interventions.

Mitochondria serve as the "powerhouses" of eukaryotic cells, generating most of the cell's energy through oxidative phosphorylation in the inner mitochondrial membrane (IMM) to produce adenosine triphosphate (ATP). Moreover, mitochondria assume a pivotal role in upholding intracellular environmental homeostasis through the regulation of reactive oxygen species (ROS), calcium ions (Ca^{2+}), and apoptosis (Zorov et al., 2014). Damaged mitochondria can increase the production of mitochondrial ROS (mtROS) (Tripathi et al., 2021), which causes oxidative damage to mitochondrial lipids, DNA, and proteins (Ashrafi and Schwarz, 2013), and also release high levels of Ca^{2+} and cytochrome C into the cytosol, triggering apoptosis (Parsons and Green, 2010). Hence, ensuring the elimination of malfunctioning mitochondria is imperative for the cell's survival.

Mitophagy stands as a form of selective autophagy that specifically targets mitochondria, and is widely considered to be the most distinctive type (Galluzzi et al., 2017). Moderate mitophagy effectively eliminates impaired mitochondria, exerting neuroprotective effects, while inadequate or excessive mitophagy may disrupt energy production and impede mitochondria-linked signaling pathways (Yang et al., 2021). Mitochondria depolarize in response to ROS, cellular senescence, nutrient scarcity, and low mitochondrial membrane potential (MMP), thereby triggering mitophagy activation. Defective mitochondria are sequestered by bilayer membrane structures, eventually resulting in the creation of autophagosomes. These specialized vesicles subsequently merge with lysosomes - cellular compartments replete with hydrolytic enzymes - culminating in mitochondrial phagocytosis (Tripathi et al., 2021). Mitophagy ensures the body's energy metabolism and tissue homeostasis by sequestering damaged mitochondria, balancing mitochondrial mass, and controlling elevated mtROS (Lin et al., 2019), which is mediated by two major pathways, namely PINK1/Parkin-dependent and PINK1/Parkin-independent pathways (Lemasters, 2005; Figure 1). Defects in mitophagy cause the accumulation of dysfunctional mitochondria, precipitating oxidative stress and various pathological conditions. Accumulating evidence substantiates the association between aberrant mitophagy processes and the onset and progression of depression, corroborated by observations of dysfunctional mitophagy in both depressed individuals and mice. Notably, certain antidepressants can alleviate depression-like behaviors in animals by regulating mitophagy. Consequently, rectifying abnormal mitophagy may present an innovative strategy for treating depression.

The objective of this review is to offer a comprehensive overview of the prevailing knowledge concerning the mechanisms of mitophagy and to deliberate on the deviations in mitophagy noted in MDD patients, along with various animal and cellular models of depression. We delineate alterations in biomarkers indicative of mitochondrial dysfunction, autophagy, and mitophagy to underscore the pivotal role played by mitophagy failure in the underlying pathological mechanisms of depression.

2. The regulation of mitophagy

2.1. The PINK1/Parkin-dependent pathway

The PINK1/Parkin-dependent pathway, governed by PTEN-induced putative kinase 1 (PINK1) and E3-ubiquitin ligase Parkin, has been extensively investigated (Clark et al., 2006). This pathway orchestrates ubiquitin-associated mitophagy, impacting numerous mitochondrial physiological processes, including mitochondrial biogenesis, dynamics, and autophagic machinery (Harper et al., 2018; Pickles et al., 2018). PINK1, a ubiquitin kinase, translocates to the IMM through translocase complexes located on both outer and inner mitochondrial membranes (OMM and IMM), contingent on membrane potential under normal conditions (Jin et al., 2010; Meissner et al., 2011). Subsequently, PINK1 undergoes cleavage by PARL, a resident rhomboid serine protease in IMM (Harper et al., 2018). The resultant N-terminal truncated PINK1 is degraded by the mitochondrial proteasome, and helps in maintaining low levels of PINK1 (Jin et al., 2010; Yamano and Youle, 2013).

The MMP decreases due to mitochondrial damage, which impairs the normal operation of transport enzymes on both IMM and OMM. This impedes PINK1 import and leads to PINK1 accumulation on the OMM. Aggregated PINK1 phosphorylates ubiquitin at S65 (p-S65-Ub) on impaired mitochondria, and consequently drawing cytoplasmic Parkin with a high p-S65-Ub affinity to form ubiquitin chains (Kane et al., 2014). Active Parkin ubiquitinates multiple OMM substrates, yielding more targets for PINK1-driven ubiquitin phosphorylation and fostering further Parkin recruitment (Pickrell and Youle, 2015; Yamano et al., 2016; Malpartida et al., 2021). Mitophagy receptors, like nuclear dot protein 52 kDa (NDP52), sequestosome 1 (SQSTM1, or P62), and optineurin (OPTN), are enlisted where ubiquitin chains have aggregated to a specific level. These mitophagy adaptors feature a ubiquitin-binding domain recognizing ubiquitin chains attached to cargoes, alongside an LC3-interacting region (LIR) enlisting phagophore membranes coated with LC3B, thus initiating mitophagy (Harper et al., 2018).

2.2. The PINK1/Parkin-independent pathway

PINK1/Parkin-independent pathways primarily hinge on receptor proteins that directly interact with LC3B and/or gamma-aminobutyric acid receptor-associated protein (GABARAP) through their LIR motifs, precipitating mitochondria elimination. These include like BCL-2 and adenovirus E1B 19-kDa interacting protein 3 (BNIP3),

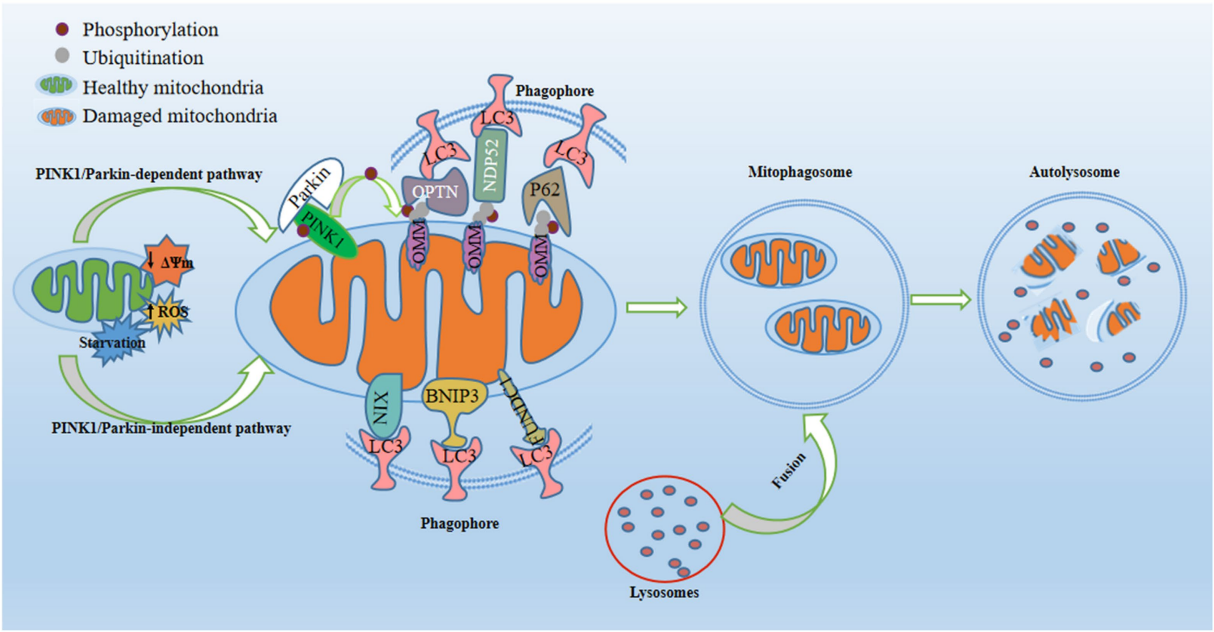

FIGURE 1
Regulatory mechanisms of mitophagy. Mitophagy, a pivotal process for maintaining mitochondrial quality, is activated in response to mitochondrial damage triggered by conditions such as starvation, diminished mitochondrial membrane potential, or increased reactive oxygen species. In the PINK1/Parkin-dependent pathway, PTEN-induced putative kinase 1 (PINK1) stabilizes on the outer mitochondrial membrane (OMM) and recruits E3-ubiquitin ligase Parkin to the OMM. This prompts the formation of phosphorylated ubiquitin at S65 (p-S65-Ub) on OMM proteins, acting as an "eat-me" signal for damaged mitochondria. Mitophagy receptors (P62, OPTN, and NDP52) recognize and bind to p-S65-Ub, consequently engaging with the phagosome through their LC3-interacting region (LIR) motif, which interacts with LC3 found on the surface of the phagosome. In the PINK1/Parkin-independent pathway, phagophores directly surround mitochondria through OMM receptors containing LIR motifs (NIX/BNIP3L, BNIP3, and FUNDC1) or by detecting exposed cardiolipin on the OMM. Once recruited, the phagophore envelops damaged mitochondria, forming mitophagosomes. Subsequently, fusion between lysosomes and mitophagosomes yields mitolysosomes, culminating in the degradation of dysfunctional mitochondria through acidic hydrolases.

B-cell leukemia/lymphoma 2 (Bcl-2) and adenovirus E1B 19-kDa interacting protein 3-like (NIX), and FUN14 domain-containing 1 (FUNDC1; Doblado et al., 2021).

2.2.1. Bcl-2 family proteins BNIP3 and NIX-mediated mitophagy

Bcl-2 family proteins play a pivotal role in OMM regulation and apoptosis control (Chipuk et al., 2006). Previous studies have shown that these proteins can trigger mitophagy through both Parkin-dependent and Parkin-independent pathways, entailing inhibition of Parkin translocation to depolarized mitochondria and relying on BNIP3 and NIX proteins (Thomas et al., 2011; Hollville et al., 2014). BNIP3 is primarily localized in mitochondria and plays an important role in regulating the fusion of autophagosomes with lysosomes (Ma et al., 2017). NIX (also known as BNIP3L) was cloned from a human placental cDNA library based on its 56% sequence identity to BNIP3 (Matsushima et al., 1998). NIX shares several features with BNIP3, encompassing interaction with BCL2 and BCL-XL, and induction of both apoptosis and autophagy (Chen et al., 1999; Schweers et al., 2007; Novak et al., 2010).

Under hypoxic or starved circumstances, NIX or BNIP3 protein levels surge, orchestrating mitophagy *via* multiple routes. Firstly, these receptors are involved in tethering mitochondria to the autophagosome by directly interacting with LC3 and/or GABARAP on the autophagosome membrane. Secondly, BNIP3 or NIX compete with Beclin-1 to bind BCL-XL. Enhanced NIX expression during erythroid differentiation disrupts existing BCL-XL–Beclin-1 complexes, liberating Beclin-1 and triggering autophagy (Thomas et al., 2011). In addition, BNIP3 can recruit Drp1 and Parkin to mitochondria by binding Parkin, then promoting mitochondrial fission to trigger mitophagy (Lee et al., 2011).

2.2.2. FUNDC1-mediated mitophagy

Previous investigations have identified FUNDC1 as a mitophagy receptor, interacting with LC3B and facilitating its recruitment to mitochondria during mitophagy (Liu et al., 2012). FUNDC1-mediated mitophagy is impeded by phosphorylation at the tyrosine 18 and serine 13 positions under normal physiological conditions. Upon hypoxia stimulation, Src is inactivated and FUNDC1 undergoes dephosphorylation, resulting in increased co-localization and interaction between FUNDC1 and LC3B. This leads to the selective incorporation of mitochondria as cargo into LC3-bound isolation membranes, consequently facilitating mitochondrial removal by LAMP1-positive autolysosomes (Liu et al., 2012; Chen et al., 2014; Lv et al., 2017).

Mitophagy is a complex, multifaceted process characterized by a multitude of molecular, organelle, and cellular interactions. These interactions synergistically contribute to ensuring the effective operation of this crucial process. Additionally, this process entails the selective removal of compromised or dysfunctional mitochondria from the cell, intricately entwined with mitochondrial function and autophagy.

3. Evidence for mitochondrial dysfunction in depression

Mitochondria serve as semi-autonomous organelles in eukaryotic cells. They are pivotal for various cellular functions and signaling cascades (Spinelli and Haigis, 2018; Belenguer et al., 2019). These organelles are also the primary sites for aerobic respiration and generate ATP to support essential neuronal processes such as neurogenesis, neurotransmission, and synaptic plasticity (Kann and Kovacs, 2007; Rangaraju et al., 2014). In the brain, mitochondria are instrumental in regulating neural activity, plasticity, and behavioral adaptation (Grimm and Eckert, 2017; Todorova and Blokland, 2017; Angelova and Abramov, 2018). Mitochondrial damage not only fails to meet the energy demands of cells, but also impairs neuronal communication and cellular resilience, potentially leading to mood disorders and mental illness (Quiroz et al., 2008; Rezin et al., 2009). This is primarily manifested by alterations in mitochondrial structure, decreased MMP levels, excessive production of ROS, reduced ATP synthesis capacity, mtDNA damage and other factors.

Preclinical and clinical data provide evidence indicating that there exists dysfunction in the mitochondria of individuals with depression as well as in animals displaying behavior similar to depression. Reports have highlighted compromised ATP production and mtDNA issues in depressed patients (Czarny et al., 2018). Specifically, these patients have exhibited diminished respiratory indices, encompassing regular respiration, uncoupled respiration, spare respiratory capacity, coupling efficiency and ATP conversion rates (Karabatsiakis et al., 2014). Meanwhile, their mtDNA copy numbers have proven to be notably higher than those of healthy individuals (Ryan et al., 2023). Furthermore, depression has been associated with increased levels of mtROS and enhanced amounts of mtDNA (Cai et al., 2015; Tripathi et al., 2021), suggesting that mitochondrial dysfunction may lead to energy depletion in the brain and contribute to the development of depression (Morava et al., 2010; Gardner and Boles, 2011).

Likewise, mitochondrial harm was noted in both afflicted animals and cells. Several animal models have been developed to mimic the depressive symptoms of patients with depression, and chronic unpredictable mild stress (CUMS), chronic restraint stress (CRS) and chronic social defeat stress (CSDS) are usually used to simulate stress-induced depression. Rodents with depression-like behaviors display increased immobility time in tail suspension test and forced swimming test (despair behavior), and decreased sucrose preference (namely anhedonia). Mice with depression, triggered by either CUMS or CMS, showed a decrease in MMP levels and a suppression of the rate of mitochondrial respiration. Moreover, their mitochondria demonstrated structural anomalies like enlargement, vacuolar degeneration, irregular inner cristae formation, or even dissolution/disappearance (Gong et al., 2011; Yuan et al., 2019; Wang et al., 2022). In addition to this, the level of ROS was growing in CUMS induced mice and microglia induced by LPS and ATP. Furthermore, the MMP was reduced in microglia induced by LPS and ATP. Decreased ATP levels and increased mtDNA copy number were also seen in Dex-induced mice (Arioz et al., 2019; Li et al., 2020; Shen et al., 2021; Wang et al., 2023).

Taken together, mitochondrial dysfunction results in escalated oxidative stress, mtDNA damage or deletions, alterations in mitochondrial fusion/fission and morphology, ultimately leading to neuronal cell demise. The process of mitophagy stands as a pivotal mechanism for upholding mitochondrial quality control through the removal of aged, dysfunctional, damaged or excessive mitochondria (Palikaras et al., 2018). This mechanism also serves to delay the onset of mitochondrial dysfunction instigated by oxidative stress and lessen the accumulation of mtDNA and ROS. In doing so, it ensures the preservation of the typical structure and function within the mitochondrial network, facilitating cellular equilibrium. Deviations in mitophagy can culminate in the accumulation of impaired mitochondria, thereby fostering depression.

4. Evidence for autophagy abnormalities in depression

Autophagy is a vital cellular mechanism present in eukaryotic cells. It is responsible for transporting damaged organelles and malformed proteins to lysosomes for degradation, thereby maintaining cellular homeostasis (Ulrich et al., 2020). Altered autophagy-related signaling pathways have been identified in patients and animal models of depression. The mammalian target of rapamycin (mTOR) serves as a critical regulator of autophagy (Winden et al., 2018). Its phosphorylated form (p-mTOR) indicates activation of the autophagic pathway (Wander et al., 2011; Fiorini et al., 2013). Autopsy findings revealed a significant reduction in the expression of mTOR and its downstream effectors (p70S6K, eIF4B, and p-eIF4B) within the prefrontal cortex of depressed patients compared to age-matched healthy controls (Jernigan et al., 2011). Autophagy is accompanied by changes in related proteins, including Beclin-1, LC3, and P62 (Wei et al., 2008; Choi et al., 2013; Cai et al., 2015; Ranjan and Pathak, 2016). The expression of autophagy genes LC3B, ATG12 and Beclin-1 was upregulated in peripheral blood mononuclear cells of depressed patients (Alcocer-Gomez et al., 2017).

In the hippocampus of depression model rats, autophagy was activated, leading to reduced p-mTOR and P62 expression, and a notable increase in Beclin-1 expression (Ning et al., 2023). Depressed rats induced by CUMS displayed elevated levels of Beclin-1 and LC3BII/I in the CA1 hippocampal region, along with increased autophagosomes observed through electron microscopy, indicating autophagy activation (Hao et al., 2013; Zhang Z. et al., 2020). On the contrary, the autophagy process was inhibited in both Lipopolysaccharide (LPS)-induced mice and astrocytes. The size and number of autophagosomes were elevated, while the LC3BII/I ratio and Beclin-1 expression dramatically rose. In contrast, P62 expression notably decreased (Li et al., 2021).

Autophagy has been confirmed to play a role in the pathogenesis and progression of depression, and certain antidepressants exert their therapeutic effects by modulating autophagic flux. Oridonin, a diterpene compound isolated from *Rabdosia rubescens* with diverse biological properties (Liu and Du, 2020), exhibits potential in alleviating depression-like behaviors. It has been observed to increase the sucrose preference rate and decrease immobility time in both the forced swimming test (FST) and tail suspension test (TST) in mice. This effect might be attributed to the upregulation of autophagy levels, evident from an elevated LC3BII/I ratio and Beclin-1 protein expression, while P62 protein was downregulated in the brains of depressed mice. A similar effect was also observed in LPS-induced astrocytes. Importantly, the autophagy-inducing agent Rapamycin synergistically enhanced oridonin-mediated upregulation of LC3BII/I, Beclin-1, and P62 protein expression. Conversely, the autophagy inhibitor 3-Methyladenine abrogated oridonin-induced promotion of autophagy (Li et al., 2021).

The tricyclic antidepressant amitriptyline can impede autophagic flux by disrupting the fusion of autophagosomes and lysosomes, possibly due to LC3BII accumulation induced by amitriptyline (20 μM), with or without NH_4Cl (an autophagosome-lysosome fusion inhibitor). A significant portion of LC3B and P62 immunoreactivities were co-localized, but not with LAMP2 (Kwon et al., 2020). Concurrently with LC3BII induction, there was a subtle increase in Beclin-1 expression observed following treatment with amitriptyline or the selective serotonin re-uptake inhibitor citalopram (Zschocke et al., 2011). Ketamine exhibited rapid-onset effects in the treatment of depression, inducing autophagy in microglia by upregulating LC3B levels and downregulating P62 protein expression. Additionally, the ketamine-induced increase in autophagy can be impeded by bafilomycin A1, an autophagy inhibitor (Lyu et al., 2022).

Both individuals and animal models with depression have been observed to display altered autophagy-associated signaling. Autophagy is a crucial cellular mechanism for eliminating damaged or dysfunctional components from cells, and its disruption can result in the accumulation of toxic substances and other harmful materials within cells. This accumulation could potentially contribute to the development of various diseases, including depression. Mitophagy, a form of selective autophagy, can also be influenced by changes in autophagy levels.

5. Evidence for impaired mitophagy in depression

5.1. Impaired mitophagy in MDD patients

Clinical research indicates that changes in mitophagy-related protein levels may relate to depression severity. Patients with depression might experience impaired mitochondria clearance, seen through higher PINK1, P62, and LC3B levels in peripheral blood nuclear cells, and lower Parkin levels (Scaini et al., 2022). The mRNA levels of PINK1, NIX, and LC3A were significantly lower in the blood of MDD patients (Weixing, 2019; Lu et al., 2023). The 18 kDa translocator protein (TSPO) has gained increased attention for its role as a crucial rate-limiting step in neurosteroidogenesis and its potential implications in the pathophysiology of stress response and related disorders (Beurdeley-Thomas et al., 2000; Pinna and Rasmusson, 2012). TSPO hinders mitophagy downstream of the PINK1/Parkin pathway by impeding crucial protein ubiquitination, and its function depends on the voltage-dependent anion channel (VDAC1; Gatliff et al., 2014). Clinical studies have demonstrated significantly elevated the TSPO density by distribution volume in the serum of patients experiencing extreme depressive episodes (Setiawan et al., 2015).

In summary, the impaired mitophagy observed in patients with depression is associated with anomalies in transcriptional processes and corresponding protein expression. Although a few clinical studies have explored this relationship, existing data are not sufficient. Additional indicators related to patient conditions are needed for further validation. Importantly, elucidating the role of mitochondrial autophagy in depression may open avenues for new therapeutic strategies for patients suffering from this condition. By conducting more extensive studies on the connection between mitochondrial autophagy and depression, researchers could acquire new insights into optimal treatment and management approaches for affected patients.

5.2. Impaired mitophagy in MDD models

Disruption of mitophagy, the selective removal of damaged mitochondria, may significantly contribute to depression-like behavior in animals, as indicated by several studies. Studies have revealed inhibited mitophagy levels in animal models of depression induced by learned helplessness (LH) and social defeat stress (SDS). These models showed substantial decreases in the expression of key proteins involved in mitophagy such as TSPO, Parkin, VDAC1, and the autophagy initiator protein Beclin-1 (Li et al., 2016; Wei et al., 2020). Similarly, mitophagy suppression was observed in the hippocampus of rats induced with chronic CUMS. This was characterized by reduced protein and mRNA expression of mitophagy-related proteins PINK1 and Parkin, along with autophagy protein Beclin-1, while protein and mRNA levels of P62 were increased (Meng, 2020). Jin et al. discovered that NIX-mediated mitophagy degradation was impaired in hippocampal neurons of CUMS-induced mice, leading to the accumulation of damaged mitochondria. This resulted in increased protein expressions of LC3BII/I, P62, and TOM20. Notably, NIX protein expression was prominently lower in the CUMS group compared to controls, whereas no differences were observed for Parkin protein (Jin et al., 2023). Similarly, the mRNA expression of NIX and LC3A was downregulated in the blood of mice induced by LPS and CSDS, while OPTN and NDP52 proteins remained unaffected in CSDS (Lu et al., 2023).

MDD is an emotional disorder associated with stress, and prolonged exposure to stress heightens susceptibility to depression (CONVERGE consortium, 2015). The social defeat stress model is commonly employed in depression research (Suzuki et al., 2021). Mitophagy and autophagy activation were observed in the hippocampus following social defeat stress, leading to increased expression of Beclin-1, ATG5, LC3B II, P62, LAMP2, PINK1, and Parkin, with the exception of TOM20, which showed reduced levels (Guo et al., 2022). Diabetes-related depression (DD) is a major complication of diabetes, and DD rats exhibited behaviors similar to depression, such as increased immobility time in the FST. Mitophagy disorders occurred in the DD rats, which results in an upregulation of related proteins LC3B, Beclin-1, and Parkin, while a downregulation of P62 and mTOR expression (Liu et al., 2021).

In BV2 cells stimulated by LPS and ATP, impaired mitophagy degradation led to elevated levels of LC3BII and prominently reduced levels of P62 in both the cytoplasm and mitochondria. Concurrently, mitochondrial levels of PINK1 and Parkin were notably decreased, while the colocalization of P62 and TOM20 through immunofluorescence increased (Han et al., 2021). Similarly, mitophagy levels were diminished in corticosterone (CORT)-induced HT22 cells, resulting in the accumulation of damaged mitochondria. This was accompanied by increased protein expressions of LC3BII/I, P62, and TOM20 (Jin et al., 2023).

Overall, these findings suggest a significant disruption in the process of selective autophagy targeting damaged mitochondria in various animal strains and cellular models. Abnormal expression of key proteins such as PINK1, Parkin, LC3B, and P62 indicates a breakdown in the cellular machinery responsible for clearing damaged mitochondria. This disruption may have profound implications for cellular health and function, providing crucial insights into the impact of impaired mitochondrial autophagy on overall cellular well-being. Moreover, these findings may have broader implications for conditions linked to impaired mitophagy, such as depression (Table 1).

TABLE 1 The alterations in mitophagy observed in depression models.

Species	The model of animals or cells	Sample Source	Experimental approaches/ methods	Molecular modifications	Expected phenotypic manifestations	Refs.
Human		Peripheral blood mononuclear cells	WB	↑PINK1, P62, and LC3B proteins ↓Parkin protein	↓The mitophagy degradation process	Scaini et al. (2022)
			RT-qPCR	↓PINK1 mRNA	↓Mitophagy level	Weixing (2019)
		Peripheral blood	RT-qPCR	↓NIX and LC3A mRNA	↓NIX-mediated mitophagy	Lu et al. (2023)
		Serum	[^{18}F] FEPPA PET	↑TSPO VT	ND	Setiawan et al. (2015)
Animal	LH mice	The mesencephalon of mice	WB	↓TSPO, PINK1, VDAC1, and Beclin-1 proteins ↑Parkin protein	↓Mitophagy level	Li et al. (2016)
	SDS mice			↓TSPO, Parkin, VDAC1, and Beclin-1 proteins	↓TSPO-mediated mitochondrial dysregulation	Wei et al. (2020)
	CUMS rat	Hippocampus	WB and RT-qPCR	↓PINK1, Parkin, Beclin-1 mRNA and proteins ↑ P62 mRNA and protein	↓PINK1/Parkin-mediated mitophagy	Meng (2020)
	CUMS mice		WB	↑LC3BII/ I ratio, P62, TOM20 proteins ↓NIX protein - Parkin protein	↓NIX-mediated mitophagy degradation	Jin et al. (2023)
	LPS mice	Blood and mPFC	WB and RT-qPCR	↓NIX and LC3A mRNA - OPTN protein -NDP52 protein	↓NIX-mediated mitophagy	Lu et al. (2023)
	CSDS mice					
	SDS mice	Hippocampus	WB	↑Beclin-1, ATG5, LC3BII, P62, LAMP2, PINK1, and Parkin proteins ↓TOM20 protein	↑PINK1/Parkin-mediated mitophagy	Guo et al. (2022)
	DD rat			↑LC3B, Beclin-1, and Parkin proteins ↓P62, mTOR protein	↑Mitophagy activation	Liu et al. (2021)
Cell	LPS and ATP-induced BV2 cell		WB and IF	Cytoplasm: ↓LC3BII, ↑P62 proteins Mitochondria: ↓LC3BII, PINK1, Parkin, and ↑P62 proteins, ↑Immunofluorescence colocalization of P62 with TOM20	↓The mitophagy degradation process	Han et al. (2021)
	CORT-induced HT22 cell		WB	↑LC3BII/ I ratio, P62, TOM20 proteins, ↓NIX protein - Parkin protein	↓NIX-mediated mitophagy degradation	Jin et al. (2023)

CSDS, chronic social defeat stress; CUMS, chronic unpredictable mild stress; CORT, corticosterone; DD, diabetes-related depression; IF, immunofluorescence; LH, learned helplessness; RT-qPCR, real-time polymerase chain reaction; SDS, social defeat stress; TSPO VT, translocator protein density by distribution volume; WB, western blot. ↑, increased; ↓, decreased; or, unchanged; ND, not determined.

5.3. Investigating the impaired mitophagy of depression for drug research

5.3.1. The effect of Chinese herbal medicine on mitophagy

Chinese herbal medicine has gained recognition for its efficacy in alleviating symptoms of depression (Butler and Pilkington, 2013). Its antidepressant effects are believed to be associated with the regulation of mitophagy levels. Wuling powder is a Chinese herbal medicine extracted from Xylaria Nigripes (Kl.) Sacc using modern fermentation technology, and was approved by China State Food and Drug Administration (Authorized Document Number: Z19990048 in Chinese medicine) for treating insomnia in 1999. It has been shown to exhibit antidepressant effects in multiple behavioral tests, with increased success rates in shuttle box escape and shortened latencies in novelty suppressed feeding test (NSF) and FST immobility time when administered at a dose of 500 mg/kg to LH mice. Wuling powder also enhanced damaged mitochondria elimination and alleviated mitophagy impairment by elevating the expression of mitophagy-related proteins TSPO, VDAC1, PINK1, and Beclin-1 in the brain, while reducing Parkin (Li et al., 2016). Xiao Jianzhong Decoction that can be used in the treatment of neurasthenia and insomnia in clinic is derived from the "treatise on febrile and miscellaneous diseases" of Zhang Zhongjing in the Eastern Han Dynasty, and has a long history of application. Xiao Jianzhong Decoction contains active compounds including paeoniflorin, cinnamic aldehyde and liquiritin that exhibit significant antidepressant effects. Administration of Xiao Jianzhong decoction effectively alleviated depression-like behaviors in CUMS-induced rats as evidenced by reduced immobility time in FST and increased total distance and time spent in open field test (OFT). This may be particularly pertinent for the upregulation of mitophagy mediated by PINK1/Parkin in the hippocampus of CUMS-induced rats through Xiao Jianzhong decoction, as evidenced by significant increases in protein expression and mRNA levels of PINK1, Parkin, and Beclin-1, along with notable reductions in P62 protein and mRNA levels (Meng, 2020). *Piper laetispicum* C. DC, a Chinese herbal remedy, demonstrated potential for alleviating depressive disorders. Clinical trials indicated that the aqueous extract of *Piper methysticum* can improve depression symptoms. G11-5 [3-(3,4-methylenedioxy-5-trifluoromethyl phenyl)-2E-propenoic acid isobutyl amide], a compound derived from the active ingredients of *Piper laetispicum* C. DC plants, has higher lipid solubility, but its toxicity still needs to be further studied. G11-5 can improve depression-like behavior in LH and SDS mice, and leads to an increased success rate for electric shock escape and greater total distance traveled during OFT movement, as well as reduced FST immobility time. Furthermore, G11-5 regulated

mitophagy levels and increasing the expression of TSPO, Parkin, VDAC1, and autophagy promoter Beclin-1 in the brain of LH mice (Wei et al., 2020).

Microglia are the resident immune surveillance cells of the central nervous system (von Bernhardi et al., 2016). The results of previous experiments have shown that inflammation mediated by activated microglia plays a crucial role in the development of MDD (Song and Colonna, 2018). Quercetin, a natural flavonoid with anti-inflammatory and antioxidant properties. It can prevent neuronal damage by promoting mitophagy and inhibiting mtROS-mediated activation of the NLRP3 inflammasome in microglia. Treatment with quercetin effectively restores impaired mitophagy in LPS-and ATP-stimulated BV2 cells, as evidenced by the upregulated expression levels of LC3BII, PINK1, and Parkin, along with the downregulated levels of P62 protein, and reduced co-localization of P62 with TOM20 observed through immunofluorescence (Han et al., 2021).

Baicalin, the primary bioactive constituent of *Scutellaria baicalensis,* has demonstrated antidepressant-like effects in various rodent models (Li et al., 2015). In CUMS-induced mice, intragastric administration of baicalin (20 mg/kg) for 4 weeks effectively ameliorated depression-like behaviors by markedly increasing the sucrose preference rate and reducing the immobility time in TST. Through investigating its molecular mechanism, baicalin was found to promote the elimination of damaged mitochondria in mice hippocampal neurons and enhance mitophagy levels mediated by NIX. This process ameliorates aberrant expression of LC3B II/I, P62, NIX, and TOM20 proteins. Additionally, baicalin markedly improved the expression of LC3BII/I, P62, and TOM20 while reducing NIX protein levels in CORT-induced HT22 cells (Jin et al., 2023).

During the course of antihypertensive treatment, *Morinda officinalis* oligosaccharides, a natural extract derived from the root of *Morinda officinalis*, have demonstrated antidepressant properties (Xu et al., 2017; Zhang et al., 2018). The depression-like behavior of CUMS-induced rats can be alleviated through the administration of *Morinda.* This intervention increases the sucrose preference rate and reduces the immobility time of rats in FST and TST. *Morinda officinalis* oligosaccharides were found to enhance autophagic flux and mitophagy in LPS-induced astrocytes, leading to a reduction in P62 levels and an increase in LC3B expression. This process facilitated the translocation of Parkin to the mitochondria and resulted in TOM20 degradation, ultimately reversing ectopic expression of LC3B and P62 (Yang et al., 2023).

In recent times, there has been a growing interest in the potential therapeutic effects of herbal remedies for depression. Research suggests that specific Chinese herbal medicines can effectively modulate levels of mitophagy, thereby positively influencing mood and alleviating depressive symptoms.

5.3.2. The effect of classic antidepressants on mitophagy

Antidepressant pharmacotherapy is an efficacious intervention for depression (Cho et al., 2016), with monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors being commonly prescribed agents (Xu et al., 2010). Fluoxetine, a pioneer of the SSRI class, has gained widespread used for its significant clinical efficacy and favorable safety profile (Perez-Caballero et al., 2014; Micheli et al., 2018; Shu et al., 2019; Hetrick et al., 2021). In a study involving CUMS-induced mice, fluoxetine was found to enhance NIX-mediated mitophagy by reducing the LC3BII/I and P62 expression while increasing NIX expression, without affecting Parkin levels (Lu et al., 2023). Additionally, the level of mitophagy was promoted by regulating the levels of mitophagy-related proteins such as TSPO, VDAC1, PINK1, and Beclin-1 in LH mice brains. However, Parkin expression was downregulated (Li et al., 2016). Astrocytes, abundant cells in the central nervous system, play a pivotal role in the pathogenesis of MDD due to their prevalence and substantial volume in the cortex and hippocampus (Kong et al., 2014; Pekny et al., 2016). Given their role in metabolic support and brain function regulation, efficient mitophagy is crucial to meet their high energy demands (Hertz et al., 2007). Fluoxetine enhances the removal of damaged mitochondria and promotes autophagic flux in astrocytes from CMS mice and primary cultured mouse astrocytes. This is evidenced by an increase in the LC3BII/I ratio and a decrease in P62 protein expression. Furthermore, fluoxetine induces mitophagy in primary astrocytes by downregulating cytoplasmic Parkin and mitochondrial TOM20 expression levels while upregulating mitochondrial Parkin expression (Shu et al., 2019). Citalopram, an SSRI, exerts protective effects on mitophagy in a transgenic mouse model of Alzheimer's disease (AD) expressing amyloid precursor protein (APP). Treatment with citalopram sensibly upregulates the mRNA levels of LC3B, ATG5, PINK1, Beclin-1 and BNIP3L in APP mice. However, it leads to significant downregulation of the expression of proteins such as PINK1, ATG5, ATG7, P62 and LC3BII/I (Reddy et al., 2021a). Moreover, it augmented the autophagic and mitophagy activity of mAPP-HT22 cells, significantly elevating mRNA levels of LC3B, ATG5, Beclin-1, PINK1 and BNIP3L while reducing protein expressions of PINK1, LC3BII, ATG5, ATG7 and P62 (Reddy et al., 2021b).

Ketamine, a frequently utilized intravenous anesthetic and analgesic in clinical practice, has recently been indicated to possess distinct advantages in antidepressant research owing to its rapid-onset antidepressant effect (Chen-Li et al., 2022). In mice exhibiting depression-like behavior induced by LPS, ketamine effectively enhanced their sucrose preference rate, reduced immobility time in FST and TST tests, and decreased feeding latency in NSFT. The LPS-induced blockage of BV2 cells' autophagic flux was reversed and early mitophagy activation was upregulated with the treatment of ketamine, which elevated the mRNA levels and protein expressions of PINK1, Beclin-1, and ATG5. Additionally, LC3BII/I and LAMP1 levels in LPS-injured BV2 cells were observed to increase, while the expression of P62 protein decreased following treatment with ketamine (Wu et al., 2022). Lu et al. proposed that NIX-mediated mitophagy could potentially serve as an antidepressant mechanism for ketamine. The study revealed that ketamine rescued TNFα-induced behavioral despair, as evidenced by a reduction in immobility time in the TST and FST, without impacting locomotion activity. Moreover, ketamine mitigated TNF-α-induced NIX deficiency in the mPFC and reversed the reduction of Beclin-1 and LC3BII proteins in the mPFC of TNF-α-treated mice. However, the knockout of NIX prevented the increase in stress-coping behaviors induced by ketamine in TNF-α-treated mice, while locomotion activity remained unaffected (Lu et al., 2023).

In simple terms, both classic and rapid antidepressants have demonstrated promising outcomes in treating depression and related illnesses like AD due to their ability to regulate mitophagy levels (Table 2).

TABLE 2 Modulation of mitophagy levels in the depression model by pharmacological interventions.

Drug type		Models	Administration	Route	Sample Source	Experimental approaches/ methods	Behavioral changes	Molecular mechanisms	Expected phenotypic manifestations	Refs.
Wuling powder	Chinese medicine compound	LH mice	500 mg/kg for 2 weeks	Gavage administration	The mesencephalon of mice	WB	Shuttle box: ↓Number of escape failures, ↓Average escape latency NSFT: ↓Feeding latency FST: ↓Immobility time	↑TSPO, PINK1, VDAC1, and Beclin-1 proteins ↓Parkin protein	↑Mitophagy level	Li et al. (2016)
Xiao Jianzhong Decoction		CUMS rat	3,600 mg/kg,7,200 mg/kg, and 14,400 mg/kg for 3 weeks		Hippocampus	WB and RT-qPCR	FST: ↓Immobility time OFT: ↑Total distance and total time of exercise	↑mRNA and protein levels of PINK1, Parkin, and Beclin-1 ↓ P62 mRNA and protein	↑PINK1/Parkin-mediated mitophagy	Meng (2020)
G11-5	Plant derivatives	LH and SDS mice	5 mg/kg, 10 mg/kg, and 20 mg/kg for 2 weeks	ND	The mesencephalon of mice	WB	Shuttle box: ↑Escape success rate FST: ↓Immobility time OFT: ↑Total distance of exercise	↑TSPO, Parkin, VDAC1, and Beclin-1 proteins	↓TSPO-mediated mitochondrial dysregulation	Wei et al. (2020)
Quercetin	Chinese herbal medicine monomer	LPS and ATP-stimulated BV2 cell	30/100 μM for 1 h			WB and IF		↑LC3BII, PINK1, Parkin protein ↓P62 protein ↓Immunofluorescence colocalization of P62 with TOM20	↑The mitophagy degradation process	Han et al. (2021)
Baicalin		CUMS mice	20 mg/kg for 4 weeks	Gavage administration	Hippocampus		SFT: ↑Sucrose preference rate TST: ↓Immobility time	↓LC3BII/I ratio, P62, TOM20 protein ↑NIX protein	↑NIX-mediated mitophagy degradation	Jin et al. (2023)
		CORT-induced HT22 cell	4 μM for 1 h			WB				
Morinda officinalis oligosaccharides		CUMS rat	100 mg/kg for 4 weeks	Gavage administration	Brain	WB and TEM	SFT: ↑Sucrose preference rate FST: ↓Immobility time TST: ↓Immobility time	↓Total protein P62, Cytoplasmic Parkin and Mitochondrial TOM20 protein ↑LC3BII/I ratio ↓Mitochondrial damage such as swollen mitochondria, adventitia rupture, cavitation	↑Autophagic flux and mitophagy level	Yang et al. (2023)
		LPS-induced astrocytes cell	2.5 and 5 mg/mL for 24 h							
Fluoxetine	SSRIs	CUMS mice	20 mg/kg for 4 weeks	Gavage administration	Hippocampus	WB	SFT: ↑Sucrose preference rate TST: ↓Immobility time	↓LC3BII/I ratio, P62, TOM20 protein ↑NIX protein	↑NIX-mediated mitophagy degradation	Lu et al. (2023)
		LH mice	10 mg/kg for 2 weeks		The mesencephalon of mice		Shuttle box: ↑Escape success rate FST: ↓Immobility time OFT: ↑Total distance of exercise	↑TSPO, Parkin, VDAC1, Beclin-1 proteins	↓TSPO-mediated mitochondrial dysregulation	Li et al. (2016)
		CMS mice	10 mg/kg for 4 weeks		Hippocampus	WB and TEM	FST: ↓Immobility time TST: ↓Immobility time	↑LC3BII/I ratio ↓ P62 protein ↓Mitochondrial damage	↑The clearance of damaged mitochondria and unblocked autophagic flux	Shu et al. (2019)
		Primary cultured mice astrocytes cell	10 μM for 1 h					Total:↑LC3BII/I ratio↓ P62 protein Cytoplasm: ↓Parkin protein Mitochondria: ↓TOM20 protein, ↑Parkin protein	↑Mitophagy induced	
Citalopram		APP mice	20 mg/kg for 4 weeks	Intraperitoneal injection	Cerebral cortex	WB and RT-qPCR		↑LC3B, ATG5, PINK1, Beclin-1, and BNIP3L mRNA ↑PINK1, ATG5, ATG7, P62, LC3BI, and LC3BII proteins	↑Mitophagy activation	Reddy et al. (2021a)
		mAPP-HT22 cell	20 μM for 24 h							Reddy et al. (2021b)

(Continued)

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TABLE 2 (Continued)

Drug type		Models	Administration	Route	Sample Source	Experimental approaches/ methods	Behavioral changes	Molecular mechanisms	Expected phenotypic manifestations	Refs.
Ketamine	N-methyl-d-aspartate receptor antagonist	LPS mice	10 mg/kg for 24 h				SFT: ↑Sucrose preference rate FST: ↓Immobility time TST: ↓Immobility time NSFT: ↓Feeding latency		↑Early mitophagy activation and autophagy flux	Wu et al. (2022)
		LPS-induced BV2 cell				WB, RT-qPCR and mRFP-GFP-LC3		↑PINK1, Beclin-1, ATG5 mRNA and proteins, LC3BII/I ratio, LAMP1 protein ↓ P62 protein ↑mRFP-GFP-labeled LC3		
		TNF-α mice	10 mg/kg was administered after TNFα treatment for 30 min	Intraperitoneal injection	mPFC	WB	FST: ↓Immobility time TST: ↓Immobility time	↑NIX, Beclin-1, and LC3BII proteins	↑NIX-mediated mitophagy	Lu et al. (2023)

CMS, chronic mild stress; CUMS, chronic unpredictable mild stress; CORT, corticosterone; FST, forced swimming test; IF, immunofluorescence; LH, learned helplessness; LPS, lipopolysaccharide; OFT, open field test; RT-qPCR, real-time polymerase chain reaction; SDS, social defeat stress; SSRIs, selective serotonin reuptake inhibitors; SFT, sucrose preference test; TNF-α, tumor necrosis factor-α; TST, tail suspension test; TEM, transmission electron microscopy; WB, western blot; mRFP-GFPLC3 probes, the tandem fluorescent-tagged LC3 probe monitoring autophagic flux based on different pH stability of mRFP; h, hour. ↑, increased; ↓, decreased; or, unchanged; ND, not determined.

6. Conclusion and prospects

Depression, a chronic illness that affects millions of people worldwide, has undergone extensive research in recent years. Although some progress has been made, current treatment options remain limited and often fail to adequately alleviate symptoms for many patients with depression. Therefore, an imperative demand for innovative therapeutic approaches exists. Based on the current research progress, we believe that restoring the level of mitophagy may be an innovative approach to improve the therapeutic effect of depression. Multiple lines of evidence reflect that mitochondrial dysfunction is linked to depression in various regions of the brain (Bansal and Kuhad, 2016; Marx et al., 2021; Hollis et al., 2022; Khan et al., 2023). Patients with mitochondrial diseases, mutations, and polymorphisms in mtDNA may undergo mood changes, cognitive function alterations, psychosis, and anxiety (Anglin et al., 2012a,b; Mancuso et al., 2013). Mitophagy is a cellular process that eliminates damaged mitochondria, effectively regulating mitochondrial quality and quantity to uphold cellular homeostasis. The regulation of mitophagy holds promising applications in the investigation and clinical management of neurological disorders like Parkinson's disease (PD) and AD (Kerr et al., 2017; Lizama and Chu, 2021). The regulation and functions of mitophagy share many similarities across PD, AD, and MDD. Furthermore, the observed alterations in mitophagy and mitochondrial function in depression propose that targeting mitophagy could be a promising therapeutic avenue.

Recent studies have shown that mitophagy plays a role in the development of depression. The mitochondrial damage caused by impaired mitophagy affects the process of mitochondrial ATP production, which impairs neuroplasticity and then negatively affects the development of depression (Bertholet et al., 2016). Mitophagy can also inhibit microglia-mediated neuroinflammation by suppressing the activation of inflammasomes, thereby attenuating depressive symptoms (Sprague and Khalil, 2009; Su et al., 2017; Taene et al., 2020). This review succinctly encapsulates recent advancements in linking mitophagy failure to the pathogenesis of MDD. Aberrant expression of the mitophagy marker PINK1 and related proteins in individuals with clinical depression underscores that mitophagy failure could potentially serve as a causal factor for MDD. Preclinical depression models also substantiate this hypothesis. These harmonious findings improve the concept that salvaging mitophagy in MDD might constitute a promising therapeutic strategy. Our review highlights that several antidepressants and effective compounds derived from Chinese herbal medicine, such as fluoxetine, ketamine, and baicalin, which have demonstrated significant amelioration of abnormal pathological and behavioral manifestations in MDD models through the induction of mitophagy. Despite some progress in exploring the relationship between mitochondrial autophagy and depression, an urgent necessity persists for a more comprehensive investigation into the evolution of this process during the progression of MDD. To gain a comprehensive understanding, it is necessary to collect more clinical data and conduct extensive preclinical studies. Only then can we hope to unravel the complex interplay between mitochondrial autophagy and depression, paving the way for potentially life-changing novel therapeutic interventions.

Author contributions

WX: writing, review and editing – original draft. WG, YG, FX, LD, SF, LF, YZ, and YH: investigation. YZ: supervision. XX and XP: project administration. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

AD	Alzheimer's disease
APP	Amyloid precursor protein
ATP	Adenosine triphosphate
Bcl-2	B-cell leukemia/lymphoma 2
BNIP3	CL-2 and adenovirus E1B 19-kDa interacting protein 3
Ca2+	Calcium ions
CMS	Chronic mild stress
CORT	Corticosterone
CSDS	Chronic social defeat stress
CUMS	Chronic unpredictable mild stress
DD	Diabetes-related depression
FST	Forced swimming test
FUNDC1	FUN14 domain-containing 1
GABARAP	Gamma-aminobutyric acid receptor-associated protein
h	Hour
IF	Immunofluorescence
IMM	Inner mitochondrial membrane
LH	Learned helplessness
LIR	LC3-interacting region
LPS	Lipopolysaccharide
MDD	Major depressive disorder
MMP	Mitochondrial membrane potential
mRFP-GFPLC3 probes	The tandem fluorescent-tagged LC3 probe monitoring autophagic flux based on different pH stability of mRFP
mtROS	Mitochondrial ROS
NDP52	Nuclear dot protein 52 kDa
NIX	B-cell leukemia/lymphoma 2 and adenovirus E1B 19-kDa interacting protein 3-like
NSF	Novelty suppressed feeding test
OFT	Open field test
OMM	Outer mitochondrial membrane
OPTN	Optineurin
PD	Parkinson's disease
PINK1	PTEN-induced putative kinase 1
p-mTOR	Phosphorylated mTOR
p-S65-Ub	Phosphorylate ubiquitin at S65
ROS	Reactive oxygen species
RT-qPCR	Real-time polymerase chain reaction
SDS	Social defeat stress
SFT	Sucrose preference test
SQSTM1	Sequestosome 1 also known as P62
SSRIs	Selective serotonin reuptake inhibitors
TEM	Transmission electron microscopy
TNF-α	Tumor necrosis factor-α
TSPO	Translocator protein
TST	Tail suspension test
VDAC1	Voltage-dependent anion channel
WB	Western blot

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EDITED BY
Katarzyna Stachowicz,
Polish Academy of Sciences, Poland

REVIEWED BY
Trevor Ronald Norman,
The University of Melbourne, Australia
Tomasz Pawlowski,
Wroclaw Medical University, Poland

*CORRESPONDENCE
Marcin Siwek,
marcin.siwek@uj.edu.pl

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TED—trazodone effectiveness in depression: a naturalistic study of the effeciveness of trazodone in extended release formulation compared to SSRIs in patients with a major depressive disorder

Dominika Dudek[1], Adrian Andrzej Chrobak[1], Anna Julia Krupa[2], Aleksandra Gorostowicz[1], Adrian Gerlich[3], Andrzej Juryk[1] and Marcin Siwek[2]*

[1]Department of Adult Psychiatry, Jagiellonian University Medical College, Cracow, Poland, [2]Department of Affective Disorders, Jagiellonian University Medical College, Cracow, Poland, [3]Department of Adult, Child and Adolescent Psychiatry, University Hospital in Cracow, Cracow, Poland

Introduction: Selective serotonin reuptake inhibitors (SSRIs) are the most often used medications to treat major depressive disorder (MDD). Despite their effectiveness in reducing depressive symptoms, several issues are associated with their use in MDD, such as limited improvement of anhedonia, emergence of emotional blunting, induction or exacerbation of insomnia, and sexual dysfunction. Due to its also devoid of the issues related to treatment noted with SSRIs. The aim of this 12-week non-inferiority naturalistic observation was to compare the effectiveness and tolerability of SSRIs and trazodone in extended release (XR) in MDD.

Methods: A total of 186 subjects were recruited, of which 92 received trazodone XR and 94 received SSRIs. Patients were allocated to trazodone XR or SSRIs, according to the attending physician based on clinical evaluation. Assessments at baseline and weeks 2, 4, 8, and 12 were conducted to evaluate the severity of depression (Montgomery–Åsberg Depression Rating Scale, clinician- and patient-rated Quick Inventory of Depressive Symptomatology—the primary endpoints of the study), anhedonia (the Snaith–Hamilton Pleasure Scale), anxiety (the Hamilton Anxiety Rating Scale), insomnia (the Athens Insomnia Scale), and therapeutic effectiveness (the Clinical Global Impression Scale).

Results: After 12 weeks, trazodone XR was more effective than SSRIs in reducing the severity of depression, anxiety, and insomnia. There was a trend for higher effectiveness of in reduction of anhedonia, which became insignificant after controlling the results for the duration of previous psychiatric treatment as a covariate. The proportion of treatment-responsive subjects in the trazodone XR group compared to SSRIs was comparable or higher. The proportion of patients achieving remission was higher in the trazodone XR arm vs. the SSRI arm.

Discussion: In summary, the results indicate that trazodone XR is effective in MDD in the "real-world" setting. Its potential superiority over SSRIs in addressing particular symptomatic dimensions should be verified in future studies.

KEYWORDS

depression, major depressive disorder, trazodone, selective serotonin reuptake inhibitor, insomnia, anhedonia, anxiety

1 Introduction

It is estimated that depression affects 10% of the general population (Qaseem et al., 2023). According to the Global Burden of Disease Study 2017, depression is the third leading cause of the burden of years lived with disability (James et al., 2018). Therefore, the optimization of depression treatment is a public health priority. The perspectives on the goals of depression treatment shift depending on its phase. Although, in the acute phase, the primary objective of the therapy is to reduce the symptoms, ideally to the level of remission, the maintenance is aimed at sustaining remission and preventing relapse. Finally, recovery is intended to restore the patient to the previous level of functioning (Qaseem et al., 2023).

As shown by Cipriani et al., there are many molecules which are effective in the treatment of major depressive disorder (MDD) (Cipriani et al., 2018). Currently, selective serotonin reuptake inhibitors (SSRIs) are the most often used and are commonly suggested as the first-line MDD treatment (Latendresse et al., 2017; APA. American Psychological Association, 2019; Marasine et al., 2021; NICE. National Institute for Health and Care Excellence, 2022; Qaseem et al., 2023). Although SSRIs are generally effective in reducing the symptoms of depression, several problems are linked to their use. Recent studies indicated that SSRIs might not only be ineffective in decreasing anhedonia (Yee et al., 2015) but they might also cause emotional blunting in as much as 50%–60% of patients (Price et al., 2009; Goodwin et al., 2017). Given that anhedonia and emotional blunting mediate the improvement of overall depression symptoms, general functioning, and quality of life, their persistence and exacerbation might hinder the achievement of recovery (McMakin et al., 2012; Siwek, 2017; Fagiolini et al., 2021). Furthermore, in some patients, SSRIs do not improve and might even worsen insomnia, which is one of the main causes of non-adherence to SSRIs in MDD (Badamasi et al., 2019). The majority of clinicians manage insomnia in patients taking SSRIs with add-on trazodone (Dording et al., 2002). Another symptom dimension of MDD, which is often either unresponsive or aggravated by SSRIs, is sexual functioning. Drug-induced sexual dysfunction is among the most common reasons for patients choosing to withdraw SSRI medication (Atmaca, 2020). Again, in order to manage sexual dysfunction due to SSRIs, physicians most often opt for the addition of another drug, bupropion (Dording et al., 2002). Yet, most depression treatment guidelines suggest antidepressant monotherapy as the preferred treatment option and rightly so as combined pharmacotherapy is linked to a higher risk of drug-to-drug interactions and adverse effects. Hence, while indisputably effective in MDD treatment, SSRIs might be inadequate or even disadvantageous in patients with pronounced anhedonia, insomnia, and sexual dysfunction or those in post-acute phases of MDD treatment.

Trazodone is an antidepressant medication classified as the serotonin 5-HT2 receptor antagonist and reuptake inhibitor (SARI). It is approved by the European Medicines Agency (Europe) and the Food and Drug Administration (United States of America) for the treatment of MDD in adult patients. Recommendations for trazodone use in clinical practice suggest that trazodone is helpful in MDD comorbid with anxiety, insomnia, and in MDD with psychomotor agitation (Cuomo et al., 2019; Albert et al., 2023; Fagiolini et al., 2023). A number of trials were conducted to compare trazodone vs. other antidepressants. Studies comparing trazodone vs. tricyclic antidepressants (TCA) in MDD treatment indicated that trazodone was comparable or superior vs. TCA; some suggested higher tolerability of trazodone (Fagiolini et al., 2012; Cuomo et al., 2019). More recent data showed that trazodone was as effective as SSRIs in MDD treatment, and more beneficial in patients with marked insomnia and was quicker to improve sleep quality (Papakostas and Fava, 2007). Trazodone was also less likely to induce sexual dysfunction than SSRIs (Khazaie et al., 2015). The comparison of trazodone with venlafaxine revealed that trazodone was more advantageous in improving insomnia, while venlafaxine offered greater effects in alleviating retardation and cognitive dysfunction, which might be due to its dual mechanism of action (serotonin and norepinephrine reuptake inhibition) (Cunningham et al., 1994; Czerwińska and Pawłowski, 2020). The majority of research on trazodone effectiveness in MDD was conducted in patients taking either immediate-release (IR) or continued-release (CR) formulation of this drug. However, in order to improve the compliance and tolerance of treatment, an extended-release formulation (also known as trazodone Contramid® once-a day— COAD) was introduced. Compared to IR and CR formulations, XR presents a preferable pharmacokinetic profile. Due to the long half-life, the plasma concentration is characterized by a slower increase, lower peak, and gradual decrease. Given that the adverse effects are more likely to occur when the peak plasma concentrations of the drug are higher and change rapidly, trazodone XR might be better tolerated than IR or CR. Unlike trazodone IR or CR, XR is dosed once daily, which makes it easier for the patient to adhere to treatment (Fagiolini et al., 2012). Recently, two randomized clinical trials (RCTs) were performed to assess the effectiveness and tolerance of trazodone XR vs. other antidepressants. The first showed that while venlafaxine offered greater overall symptom reduction after 8 weeks of treatment, trazodone XR was more effective in achieving early response after 1 week of therapy (Fagiolini et al., 2020). The second indicated that trazodone XR was as effective as clomipramine but better tolerated (Buoli et al., 2019). Although RCTs are the "gold standard" of evidence-based assessments of drug effectiveness and tolerance, their results are not easily translated into every day clinical practice as due to strict inclusion criteria only 20% of patients are

eligible (Preskorn et al., 2015). Thus, naturalistic observations are necessary to verify the effectiveness and tolerability of drugs in "real-world" patients. We have previously published the pilot study, which indicated that trazodone is not inferior to SSRIs in achieving the treatment response and remission in MDD patients (Siwek et al., 2023). Nonetheless, these results were preliminary and needed to be corroborated in a larger group of patients.

The aim of this study was to compare the effectiveness and tolerability of trazodone XR vs. SSRIs.

2 Materials and methods

2.1 Study design

This was a single-center, open-label, non-inferiority naturalistic observation comparing the effectiveness and tolerability of trazodone XR vs. SSRIs. For this study, patients with MDD diagnosed according to DSM-5 (Diagnostic and Statistical Manual of Mental Disorders 5th edition) criteria were included. The inclusion criteria are as follows: age 18–65 years, diagnosis of a first MDD episode according to DSM-5, or an acute MDD episode in patients diagnosed with recurrent depression. The exclusion criteria were as follows: current or a past episode of drug-resistant depression; diagnosis of bipolar disorder, persistent mood disorder, organic mood disorder, and schizoaffective disorder; substance use disorder (with the exception of nicotine and caffeine); pregnancy or breastfeeding; non-consensual treatment; severe somatic diseases associated with renal, hepatic, circulatory, or respiratory failure; a diagnosis of severe neurological disease (multiple sclerosis, neurodegenerative diseases, Parkinson's disease, epilepsy, and dementia); and pharmacotherapy with clinically significant cytochrome P450 inducers, e.g., rifampicin, glucocorticosteroids, phenytoin, and carbamazepine.

Patients were allocated to groups receiving trazodone XR (150–300 mg/d) or SSRIs (sertraline 50–200 mg/d, citalopram 20–40 mg/d, escitalopram 10–20 mg/d, and paroxetine 20–60 mg/d) in monotherapy. The choice of the drug and its dose was made by the attending physician after thorough analysis of the clinical condition, potential comorbidities, and drug interactions. As in our pilot study, selection of the antidepressant was based on the clinical manifestation of MDD and previous treatment history, following the guidelines of the Polish Psychiatric Association and the National Consultant for Adult Psychiatry in Poland (Samochowiec et al., 2021; Siwek et al., 2023).

The study was approved by the Bioethics Committee of the Jagiellonian University in Krakow (approval No. 1072.6120.113.2021). All participants signed informed written consent forms.

2.2 Assessments

Basic socio-demographic data were collected by the attending physician at the enrollment. Clinical evaluation was performed at baseline and after 2, 4, 8, and 12 weeks of treatment. Each assessment included measures of overall depression severity, anxiety, anhedonia, and insomnia, which were conducted with the following:

- Depression rating scales: the Montgomery–Åsberg Depression Rating Scale (MADRS)—clinician-rated; the Quick Inventory of Depressive Symptomatology (QIDS)—clinician- (QIDS-CR) and self-rated (QIDS-SR),
- Clinician-rated tool measuring anxiety: the Hamilton Anxiety Rating Scale (HAM-A),
- Self-rated questionnaire to assess anhedonia: the Snaith–Hamilton Pleasure Scale (SHAPS),
- Self-rated scale to evaluate sleep disturbance: the Athens Insomnia Scale (AIS),
- Clinician-rated measure of overall symptom severity and improvement: the Clinical Global Impression Scale (CGI).

Changes in overall severity of depression measured by MADRS, QIDS-CR, and QIDS-SR scores across the subsequent time points were the primary endpoints of this study. The treatment response was defined as ≥50% reduction of symptoms, as assessed with QIDS, QIDS-SR, and MADRS or CGI-I score ≤2 ("Very Much Improved" or "Much Improved"), and the remission was defined as scores below 6 points on the QIDS-CR and QIDS-SR scale or below 10 on MADRS. Both treatment response and remission were assessed after 12 weeks of treatment duration.

2.3 Statistical analysis

Statistical analysis was carried out on data from 160 subjects who participated in the study. General group characteristics and baseline clinical measures were compared with the use of a *t*-test in the case of quantitative variables and $\chi 2$ in the case of qualitative variables between the groups receiving trazodone XR or SSRIs. The Shapiro–Wilk test was used to assess the distribution of quantitative variables. Qualitative variables were presented as proportions, and quantitative variables, as mean and standard deviations.

To evaluate the changes in the total scores of MADRS, QIDS-CR, and QIDS-SR (primary endpoints of the study), and HAM-A, AIS, and SHAPS (secondary endpoints), a linear mixed-effects model (MMRM — mixed model for repeated measures) was built. The analysis was performed via the lmer function from the lme4 package in R [version R 4.2.1 (RCore Team, 2022)]. The model included time points of measurement (0, 2, 4, 8, and 12 weeks) and the treatment group (trazodone XR or SSRIs) as fixed effects and participants as a random effect (with restricted maximum likelihood [REML] being applied). Effects of time, treatment, and time × treatment (interaction) on the dependent variable (MADRS, QIDS-CR, QIDS-SR, HAM-A, AIS, and SHAPS scores) were evaluated. Effect size was calculated as partial-eta squared for an interaction. Between-group comparisons (trazodone XR vs. SSRIs) were calculated for the estimated marginal means at each timepoint. Additional analysis was performed with the same method for all the outcomes with the duration of the previous psychiatric treatment included as a covariate in the model.

Internal consistency reliability was previously assessed in the pilot study (Siwek et al., 2023).

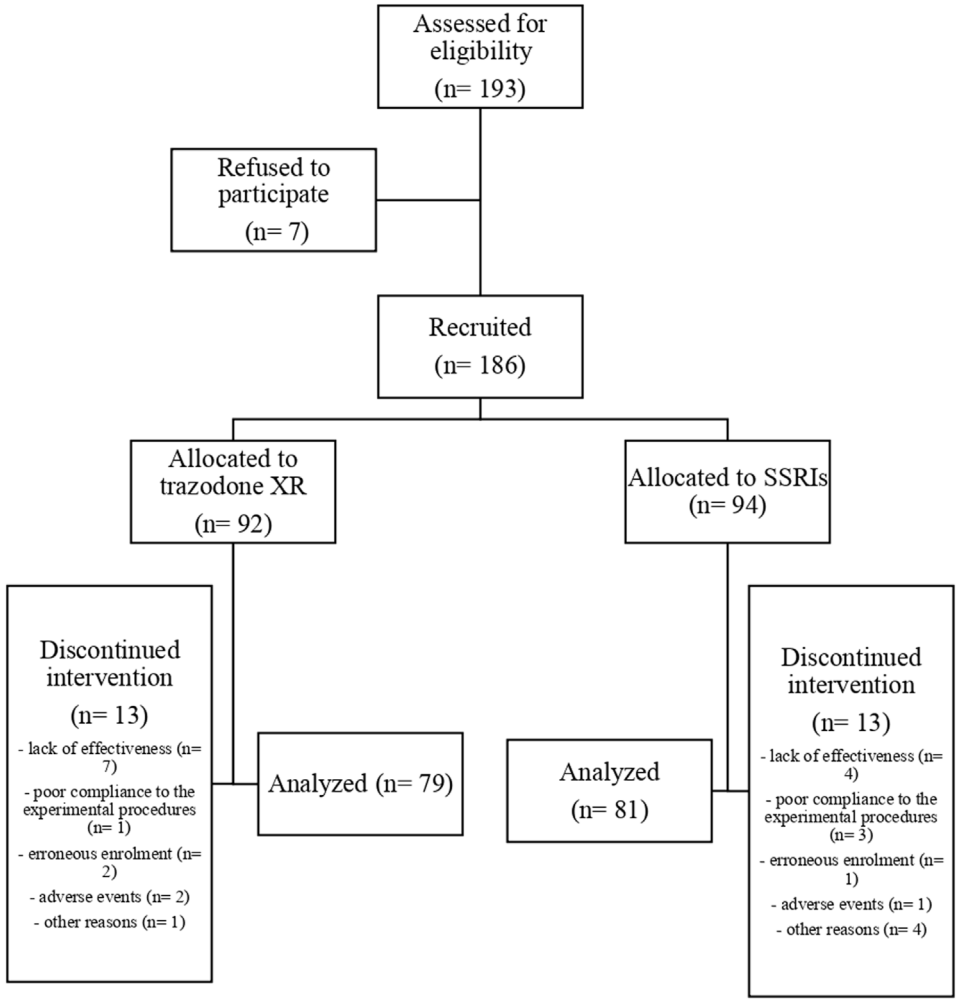

FIGURE 1
Flow chart of the study.

Proportions of treatment response and remission, as assessed with QIDS-CR, QIDS-SR, and MADRS, were compared between trazodone XR and SSRIs with the use of the $\chi 2$ test. Statistical significance was defined as a two-sided p-value of <0.05.

3 Results

3.1 Group characteristics

The flow chart of the study is presented in Figure 1. Comparisons of general group characteristics are presented in Table 1. The groups were comparable regarding sex, age, BMI, alcohol consumption, and presence of somatic comorbidities. The proportion of subjects who smoked was significantly higher in patients treated with trazodone XR vs. SSRIs. The duration of previous psychiatric treatment was longer in the subjects receiving trazodone XR vs. SSRIs. The severity of depression was comparable between the groups when assessed by MADRS and QIDS-SR; a trend for higher severity of depression was observed in the trazodone XR group vs. SSRIs group when evaluated by QIDS-CR (Table 1).

3.2 Outcomes

The results of the MMRM models for each outcome measure are presented in Table 2. The effect of an interaction between time and the treatment type was statistically significant for scores in MADRS [$F(4, 529.03) = 5.386$, $p < 0.001$], QIDS-CR [$F(4, 535.65) = 6.405$, $p < 0.001$], QIDS-SR [$F(4, 512.35) = 6.061$, $p < 0.001$], HAM-A [$F(4, 544.52) = 4.889$, $p < 0.001$], AIS [$F(4, 553.15) = 15.755$, $p < 0.001$], and SHAPS [$F(4, 550.86) = 2.495$, $p = 0.04$]. Effect sizes for the time × treatment interaction (measured by the partial-eta squared, $\eta 2$) were moderate for AIS ($\eta 2 = 0.1$) and small for QIDS-CR ($\eta 2 = 0.05$), QIDS-SR ($\eta 2 = 0.05$), MADRS ($\eta 2 = 0.04$), HAMA ($\eta 2 = 0.03$), and SHAPS ($\eta 2 = 0.02$) (Table 2).

The estimated marginal means for each outcome measure are displayed in Table 3, separately at each timepoint (baseline, 2, 4, 8, and 12 weeks) with appropriate p-values for comparisons between

TABLE 1 Baseline group characteristics.

	SSRI (n = 81)	Trazodone XR (n = 79)	p-value
Sex (% female)	62.2%	50,65%	0.191[a]
Age (in years): mean (SD)	34.9 (12.9)	34.4 (12.0)	0.917[b]
BMI (in kilograms/m^2): mean (SD)	23.9 (5.04)	24 (3.45)	0.907[b]
Duration of previous psychiatric treatment (in months)	21.3 (65.2)	32.6 (64.6)	0.046[b]
Alcohol consumption (% yes)	65.3%	71.8%	0.506[a]
Smoking (% yes)	7.2%	23.1%	0.018[a]
Somatic comorbidities (% yes)	28.1%	33.7%	0.582[a]
MADRS: mean (SD)	27.2 (7.41)	28.8 (7.26)	0.590[b]
QIDS-CR: mean (SD)	13.8 (4.07)	14.2 (4.38)	0.054[b]
QIDS-SR: mean (SD)	14.5 (4.59)	15.7 (4.72)	0.841[b]
SHAPS: mean (SD)	6.64 (4.48)	6.69 (4.29)	0.282[b]
HAMA: mean (SD)	20.6 (7.8)	21.5 (7.4)	0.452[b]
AIS: mean (SD)	10.4 (4.94)	13.7 (5.52)	0.161[b]

AIS, Athens Insomnia Scale; CGI-S, Clinical Global Impression Scale severity; HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; QIDS-CR, Quick Inventory of Depressive Symptomatology—clinician-rated; QIDS-SR, Quick Inventory of Depressive Symptomatology—self-rated; SD, standard deviation; SHAPS, Snaith–Hamilton Pleasure Scale; XR, extended-release formulation.
[a]Chi-squared test.
[b]Independent-sample *t*-test.

TABLE 2 Results of mixed-effect model–significance levels and effect sizes (partial-eta squared) for all outcomes.

	Time effect, p	Treatment effect, p	Time × treatment effect, p	Partial-eta squared for interaction (with 95% CI)
MADRS	<0.001	0.308	<0.001	0.04 (0.01–0.07)
QIDS-CR	<0.001	0.019	<0.001	0.05 (0.01–0.08)
QIDS-SR	<0.001	0.566	<0.001	0.05 (0.01–0.08)
HAM-A	<0.001	0.299	<0.001	0.03 (0.01–0.06)
AIS	<0.001	0.186	<0.001	0.1 (0.06–0.15)
SHAPS	<0.001	0.164	0.04	0.02 (0.00–0.04)
BMI	0.869	0.856	0.821	<0.001 (0.00–0.01)

AIS, Athens Insomnia Scale; HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; QIDS-CR, Quick Inventory of Depressive Symptomatology—clinician-rated; QIDS-SR, Quick Inventory of Depressive Symptomatology—self-rated; SHAPS, Snaith–Hamilton Pleasure Scale.

SSRIs and trazodone. Statistically significant differences between SSRIs and trazodone XR in favor of trazodone were noted in MADRS at 8 weeks (11.2 vs. 8.03, $p = 0.039$) and at 12 weeks (11.06 vs. 5.99, $p = 0.001$); QIDS-CR (6.71 vs. 3.21, $p < 0.001$), QIDS-SR (7.66 vs. 5, $p = 0.003$), and SHAPS (4.42 vs. 2.56, $p = 0.011$) at 12 weeks; HAM-A at 8 weeks (6.98 vs. 4.27, $p = 0.03$) and at 12 weeks (7.46 vs. 3.7, $p = 0.003$); and AIS at baseline (10.42 vs. 13.73, $p < 0.001$), at 4 weeks (7.68 vs. 5.72, $p = 0.014$), at 8 weeks (6.11 vs. 4.39, $p = 0.034$), and at 12 weeks (7.04 vs. 3.88, $p < 0.001$) (Table 3).

The results of the MMRM models for each assessed outcome, with the duration of previous psychiatric treatment as a covariate, are depicted in Table 4. There was a statistically significant effect of the interaction between time and treatment type for the scores in MADRS [F (4, 471.9] = 5.79, $p < 0.001$), QIDS-CR [F (4, 479.9) = 14.02), $p < 0.001$], QIDS-SR [F (4, 453.4) = 5.07), $p < 0.001$], HAM-A [F (4, 485.4) = 4.8), $p < 0.001$], and AIS [F (4, 490.9) = 14.01), $p < 0.001$]. The effect of the interaction between time and the treatment type for the scores in the SHAPS showed a trend which did not reach the level of statistical significance [F (4, 491.9) = 2.24, $p = 0.06$]. The effect sizes for the time–treatment interaction (measured by the partial-eta square, η2) were moderate for the AIS (η2 = 0.1) scale and small for the MADRS (η2 = 0.04), QIDS-CR (η2 = 0.05), QIDS-SR (η2 = 0.05), and HAM-A (η2 = 0.03) scales (Table 4).

Table 5 and Figure 2 show the comparison of proportions of patients achieving treatment response and remission in SSRIs vs trazodone XR groups, as assessed after 12 weeks. As measured by QIDS-CR, the proportion of participants achieving treatment response was higher in the trazodone XR vs. SSRIs group. As

TABLE 3 Between-group comparisons for each timepoint.

	Baseline emmean (95% CI)			2 weeks emmean (95% CI)			4 weeks emmean (95% CI)			8 weeks emmean (95% CI)			12 weeks emmean (95% CI)		
	SSRI	T-XR	p-value	SSRI	T-XR	p-value	SSRI	T-XR	p-value	SSRI	T-XR	p-value	SSRI	T-XR	p-value
MADRS	27.29 (25.3–29.3)	28.74 (26.69–30.8)	0.318	19.19 (17.15–21.2)	20.6 (17.97–22.2)	0.556	12.77 (10.73–14.8)	13.41 (11.28–15.5)	0.67	11.22 (9.11–13.3)	8.03 (5.86–10.2)	0.039	11.06 (8.94–13.2)	5.99 (3.78–8.2)	0.001
QIDS-CR	13.69 (12.54–14.83)	14.2 (13.02–15.39)	0.537	10.16 (8.98–11.33)	10.1 (8.91–11.29)	0.946	7.31 (6.14–8.48)	5.91 (4.77–7.16)	0.116	6.57 (5.36–7.77)	3.79 (2.55–5.02)	0.002	6.79 (5.58–8.00)	3.21 (1.95–4.47)	<0.001
QIDS-SR	14.26 (13.08–15.43)	15.6 (14.3–16.9)	0.133	10.86 (9.68–12.04)	12.17 (10.95–13.39)	0.13	8.69 (7.52–9.87)	8.07 (6.83–9.32)	0.476	7.4 (6.21–8.59)	6.21 (4.94–7.48)	0.178	7.66 (6.45–8.88)	5 (3.71–6.29)	0.003
HAM-A	20.51 (18.87–22.15)	21.34 (19.59–23.09)	0.499	12.35 (10.68–14.01)	13.18 (11.46–14.9)	0.495	7.45 (5.77–9.13)	7.66 (5.92–9.39)	0.865	6.98 (5.3–8.67)	4.27 (2.5–6.04)	0.03	7.46 (5.57–9.18)	3.7 (1.88–5.51)	0.003
AIS	10.42 (9.37–11.47)	13.73 (12.64–14.81)	<0.001	9.07 (7.98–10.15)	8.9 (7.82–9.98)	0.826	7.68 (6.61–8.76)	5.73 (4.6–6.86)	0.014	6.11 (5.03–7.19)	4.39 (3.23–5.55)	0.034	7.04 (5.92–8.16)	3.88 (2.7–5.05)	<0.001
SHAPS	6.62 (5.69–7.55)	6.65 (5.67–7.63)	0.969	5.29 (4.33–6.25)	5.65 (4.69–6.62)	0.601	4.42 (3.44–5.4)	3.4 (2.38–4.41)	0.154	3.67 (2.71–4.64)	2.69 (1.66–3.72)	0.172	4.43 (3.43–5.43)	2.56 (1.51–3.6)	0.011
BMI	23.9 (22.9–24.9)	24 (22.9–25)	0.907	23.8 (22.8–24.8)	23.9 (22.9–24.9)	0.931	23.8 (22.8–24.8)	24 (22.9–25)	0.807	23.8 (22.8–24.8)	24 (22.9–25)	0.842	23.8 (22.8–24.8)	23.9 (22.9–25)	0.865

Values are presented as estimated marginal means with 95% confidence intervals. Emmean, estimated marginal mean. AIS, Athens Insomnia Scale; HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; QIDS-CR, Quick Inventory of Depressive Symptomatology—clinician-rated; QIDS-SR, Quick Inventory of Depressive Symptomatology—self-rated; SHAPS, Snaith–Hamilton Pleasure Scale, T-XR, trazodone extended-release formulation.

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TABLE 4 Results of the mixed-effect model, with the duration of previous psychiatric treatment as a covariate, showing the significance levels and effect sizes (partial-eta squared) for all outcomes.

	Treatment effect, p	Time effect, p	Time × treatment effect, p	Partial-eta squared for interaction (with 95% CI)
MADRS	0.590	<0.001	<0.001	0.04 (0.01–0.07)
QIDS-CR	0.054	<0.001	<0.001	0.05 (0.01–0.08)
QIDS-SR	0.841	<0.001	<0.001	0.05 (0.01–0.08)
HAM-A	0.452	<0.001	<0.001	0.03 (0.01–0.07)
AIS	0.161	<0.001	<0.001	0.10 (0.06–0.15)
SHAPS	0.282	<0.001	0.064	0.02 (0.00–0.04)

MADRS, Montgomery–Asberg Depression Rating Scale; HAM-A, Hamilton Anxiety Rating Scale; QIDS-CR, Quick Inventory of Depressive Symptomatology—clinician-rated; QIDS-SR, Quick Inventory of Depressive Symptomatology, self-rated; SHAPS, Snaith–Hamilton Pleasure Scale; AIS, Athens Insomnia Scale.

TABLE 5 Comparison of frequencies of therapeutic response, remission (measured by QIDS-CR, QIDS-SR, and MADRS scores), and clinical improvement (measured by CGI-I) between patients treated with SSRI and trazodone XR after 12 weeks of treatment.

	SSRI	Trazodone XR	p-value
Treatment response (≥50% reduction of the MADRS score after 12 weeks), % of patients	67.2	81.3	0.082
Treatment response (≥50% reduction of the QIDS-CR score after 12 weeks), % of patients	56.5	81.4	0.006
Treatment response (≥50% reduction of the QIDS-SR score after 12 weeks), % of patients	53,3	66.6	0.24
CGI-I score 1 or 2 after 12 weeks of treatment, % of patients	81.4	83	0.113
Remission (<10 points in MADRS) after 12 weeks, % of patients	48	78.3	0.012
Remission (<6 points in QIDS-CR) after 12 weeks, % of patients	52.2	78.7	0.003
Remission (<6 points in QIDS-SR) after 12 weeks, % of patients	43.3	65.5	0.021

CGI-I, Clinical Global Impression Scale—improvement; MADRS, Montgomery–Asberg Depression Rating Scale; QIDS-CR, Quick Inventory of Depressive Symptomatology—clinician-rated; QIDS-SR, Quick Inventory of Depressive Symptomatology—self-rated.

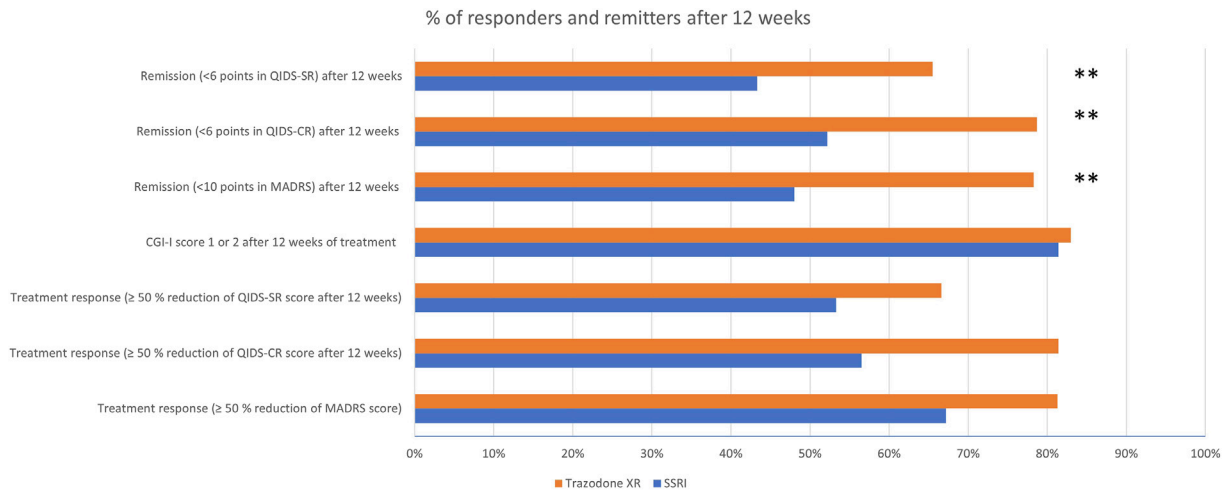

FIGURE 2
Proportions of patients achieving treatment response and remission in in SSRIs vs. trazodone XR groups.

assessed by MADRS, QIDS-SR, and CGI-I, no statistically significant differences in the proportion of individuals achieving treatment response between the SSRIs and trazodone XR groups were noted. Total scores of MADRS, QIDS-CR, and QIDS-SR indicated that the proportion of participants achieving remission was higher in the trazodone XR vs. SSRI group (Table 5; Figure 2).

4 Discussion

The results showed that both SSRIs and trazodone XR were effective in reducing the overall symptoms of depression, anxiety, insomnia, and anhedonia. No significant effects of the treatment on BMI were noted in neither of the treatment groups. The discontinuation levels were 16.46% in the trazodone XR group and 16.05% in the SSRI group.

Baseline comparisons showed that both treatment arms were similar regarding the severity of anxiety, insomnia, and anhedonia. The baseline scores of depression varied depending on the tool used for evaluation; two scales indicated that levels of depression were comparable in both groups, while one showed a trend for higher levels of depression in the trazodone XR group vs. SSRIs group which did not reach statistical significance. There is a plethora of depression clinical presentations which vary greatly, and the tools used to measure the severity of depression are considerably dissimilar in the range of assessed symptoms. In addition, it is known that clinician and self-rated tools are not interchangeable in evaluating depressive symptoms, even despite the same content, and using either clinician or self-assessed scales might not provide a thorough evaluation of the clinical picture. It is, therefore, highly advisable to use more than one tool to measure affective symptoms and include both patient- and clinician-rated scales in order to increase the credibility and replicability of results (Uher et al., 2012; Fried, 2017; Chrobak et al., 2018).

Moreover, the MMRM analysis indicated that trazodone XR was more effective than SSRIs in reducing the levels of depression measured by MADRS, QIDS-SR, and QIDS-CR; anxiety assessed by HAM-A; and insomnia evaluated by AIS; these results remained significant after controlling for the duration of previous psychiatric treatment as a covariate. The initial MMRM analysis suggested that trazodone XR was also more effective in improving anhedonia assessed by SHAPS, but after controlling for the duration of previous psychiatric treatment, this trend did not reach statistical significance. Relatively high treatment response and remission rates were noted in both study arms. The estimated marginal means showed that, compared to SSRIs, the benefits of trazodone XR treatment were noticeable after 4 weeks, regarding insomnia, and 8 weeks, regarding the severity of depression and anxiety.

The proportion of treatment-responsive subjects in the trazodone XR group compared to the SSRI group was higher when assessed by QIDS-CR (81.4% vs. 56.5%), or comparable when evaluated with MADRS (81.3% vs. 67.2%), QIDS-SR (66.6% vs. 53.3%), or CGI-I (83% vs. 81.4%). The proportion of patients achieving remission was statistically significantly higher in the trazodone XR arm vs. SSRI arm, as assessed with MADRS (78.3% vs. 48%), QIDS-CR (78.7% vs. 52.2%), and QIDS-SR (65.5% vs. 43.3%). In contrast, in the largest to date "real-world" study on the effectiveness of antidepressant treatment (citalopram), STAR*D treatment response was noted in 47% and remission in 28%–33% of participants. Several factors might have influenced our results (Trivedi et al., 2006). First, this was a single-centered study performed in a university psychiatric clinic, while STAR*D was a multi-centered study performed in both psychiatric and primary care settings. Second, patients enrolled in the STAR*D study had a mean duration of illness of 15 years, while in our study, the mean duration of illness was 21.3 months in the SSRI group and 32.6 in the trazodone XR group. Third, the inclusion criteria in our trial were stricter than in STAR*D, i.e., we did not include subjects with persistent mood disorder, while in the former study, these patients constituted approximately 25% of the study sample; our observation excluded individuals with substance abuse (other than caffeine of nicotine), while in the STAR*D study, participants with alcohol or drug dependence accounted for nearly 20% of the sample. These factors could explain the differences in the rates of treatment response and remission in our observation, given that a longer duration of depressive symptoms and/or substance abuse are liked to lower treatment effectiveness of antidepressant therapy (Ghio et al., 2014; Agabio et al., 2018). Our results are consistent with the previous findings, suggesting that trazodone (CR or IR) is no less effective than fluoxetine (Falk et al., 1989; Beasley et al., 1991), paroxetine (Kasper et al., 2005), or sertraline (Munizza et al., 2006) in MDD and more beneficial in improving insomnia (Papakostas and Fava, 2007). On the other hand, a more recent RCT indicated that venlafaxine XR was more effective than trazodone XR in achieving remission of depressive symptoms, while the results regarding reduction of depression severity and achievement of treatment response were inconsistent, indicating comparable or superior effectiveness of venlafaxine XR vs. trazodone XR. In congruence with this study, we observed that the reduction of depressive symptoms occurs earlier in the course of treatment in trazodone XR vs. SSRI-treated subjects (Fagiolini et al., 2020). Noteworthy, all the previous studies comparing trazodone to SSRIs were double-blind clinical trials, and all, but one, used only clinician-rated tools to assess treatment outcomes, especially the Hamilton Depression Rating Scale, MADRS, and/or CGI. None administered specific tools to evaluate the changes in insomnia or anhedonia. Adding to the pilot results of this study (Siwek et al., 2023), we noted that compared to SSRIs, trazodone XR was more effective in improving not only depression and insomnia but also anxiety. Although the pilot showed no significant differences in the levels of treatment response and remission, the analysis of the complete sample indicated that trazodone XR was more effective than SSRIs in achieving the remission of depressive symptoms. The results were inconsistent regarding the levels of treatment response as one of the scales suggested higher effectiveness of trazodone XR vs. SSRIs (QIDS-CR), while the three others did not (MADRS, QIDS-SR, and CGI-I).

The novelty of our work lies in several methodological attributes: 1) the use of three tools assessing depression severity, both clinician- and patient-rated, which provide a more thorough assessment of trazodone XR effectiveness in reducing overall depression severity; 2) the use of specific scales to measure the severity of different symptom dimensions such as AIS, HAM-A, and SHAPS, and which offer more precise knowledge on the effectiveness of trazodone XR in particular symptomatic dimensions, and 3) the choice of naturalistic observation design, which is more easily translated to the "real-life" settings than RCT. Indeed, the focused assessment of anhedonia is an important advancement in the evaluation of depression clinical presentation as it is known that improvement in positive affect and hedonic tone is more relevant to functional remission than changes in negative affect, which are the focus of the depression assessment tools (HAM-D) (Demyttenaere et al., 2021). Moreover, the thorough measurement of insomnia is of significant value as it

is one of the most common reasons for treatment discontinuation (Badamasi et al., 2019) and resistance (Wade, 2006).

Our work has several limitations. The naturalistic, open-label design of the study and lack of randomization may have contributed to the dissimilarity of treatment arms. Nonetheless, this did not obstruct the potential of this work to show the non-inferiority of trazodone XR vs. SSRIs (as the trazodone XR arm presented a longer previous psychiatric treatment duration, which could potentially lower the effectiveness of the drug). Other potentially confounding factors were the single-center design, differences in antidepressant doses, and inclusion of various SSRIs in the same group. Because of this, the results require replications in studies with more robust methodology. However, this does not hamper the advances provided in our work, which are due to a more thorough assessment of the depressive symptomatology. Given the non-inferiority design, we might only dispute on the comparableness of trazodone XR vs. SSRIs, but the speculations on its superiority to SSRIs remain to be verified in future trials.

5 Conclusion

In summary, our results demonstrate that trazodone XR is a valuable MDD treatment option as SSRIs. The potential superiority of trazodone XR vs. SSRIs in improving overall depression, anhedonia, and insomnia, and achieving remission should be further evaluated in future studies.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Bioethics Committee of the Jagiellonian University in Krakow. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

DD: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, and Writing–review and editing. AC: Data curation, Formal analysis, Investigation, Methodology, project administration, software, and writing–review and editing. AK: investigation, Writing–original draft, and Writing–review and editing. AGo: Data curation, Formal analysis, Investigation, Methodology, Software, and Writing–review and editing. AGe: Data curation, Investigation, and Writing–review and editing. AJ: Investigation and Writing–review and editing. MS: Investigation, Writing–review and editing, Conceptualization, Funding acquisition, Methodology, Project administration, Resources, and Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Magdalena Sowa-Kucma,
University of Rzeszow, Poland

REVIEWED BY
Amanda Bertollo,
Federal University of the Southern Frontier, Brazil
Erika Estrada-Camarena,
National Institute of Psychiatry Ramon de la Fuente Muñiz (INPRFM), Mexico

*CORRESPONDENCE
Rong Zhang,
zhangrong@gzucm.edu.cn
Jinlan Zhao,
zhaojinlan@gzucm.edu.cn

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Si-Ni-San alleviates early life stress-induced depression-like behaviors in adolescence via modulating Rac1 activity and associated spine plasticity in the nucleus accumbens

Lihong Ye[1], Jiayi Wu[2], Zuyi Liu[1], Di Deng[1], Shasha Bai[1], Lei Yang[1], Yao Xuan[1], Zehao Liu[1], Yafei Shi[2], Zhongqiu Liu[1], Rong Zhang[1]* and Jinlan Zhao[1]*

[1]Guangdong Provincial Key Laboratory of Translational Cancer Research of Chinese Medicines, Joint International Research Laboratory of Translational Cancer Research of Chinese Medicines, International Institute for Translational Chinese Medicine, School of Pharmaceutical Sciences, Guangzhou University of Chinese Medicine, Guangzhou, China, [2]School of Fundamental Medical Science, Guangzhou University of Chinese Medicine, Guangzhou, China

Background: Early life stress (ELS) is a major risk factor for depression in adolescents. The nucleus accumbens (NAc) is a key center of the reward system, and spine remodeling in the NAc contributes to the development of depression. The Si-Ni-San formula (SNS) is a fundamental prescription for treating depression in traditional Chinese medicine. However, little is known about the effects of SNS on behavioral abnormalities and spine plasticity in the NAc induced by ELS.

Purpose: This study aimed to investigate the therapeutic effect and the modulatory mechanism of SNS on abnormal behaviors and spine plasticity in the NAc caused by ELS.

Methods: We utilized a model of ELS that involved maternal separation with early weaning to explore the protective effects of SNS on adolescent depression. Depressive-like behaviors were evaluated by the sucrose preference test, the tail suspension test, and the forced swimming test; anxiety-like behaviors were monitored by the open field test and the elevated plus maze. A laser scanning confocal microscope was used to analyze dendritic spine remodeling in the NAc. The activity of Rac1 was detected by pull-down and Western blot tests. Viral-mediated gene transfer of Rac1 was used to investigate its role in ELS-induced depression-like behaviors in adolescence.

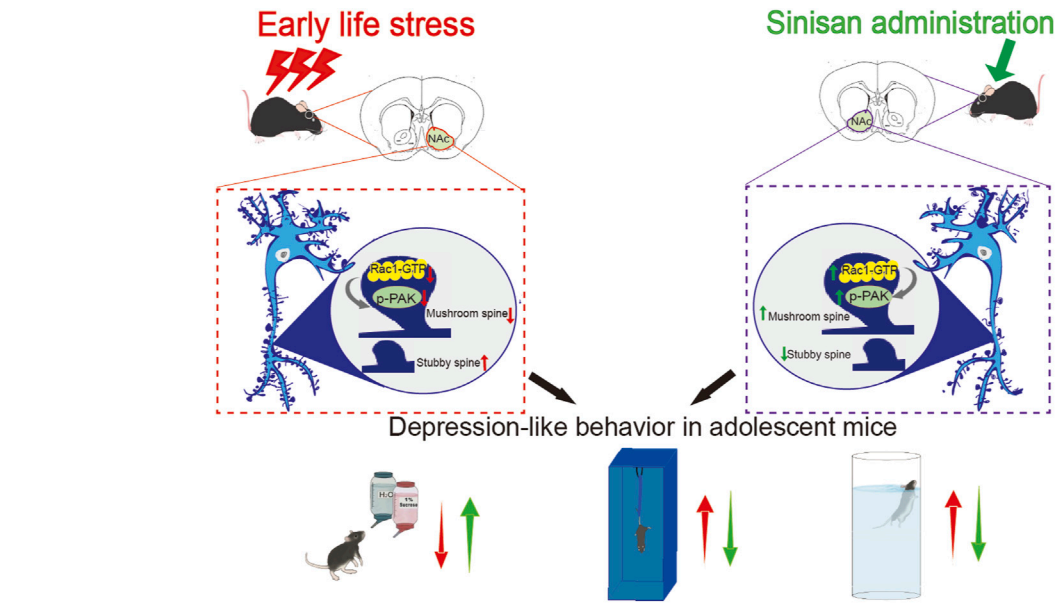
Results: ELS induced depression-like behaviors but not anxiety-like behaviors in adolescent mice, accompanied by an increase in stubby spine density, a decrease in mushroom spine density, and decreased Rac1 activity in the NAc. Overexpression of constitutively active Rac1 in the NAc reversed depression-related behaviors, leading to a decrease in stubby spine density and an increase in mushroom spine density. Moreover, SNS attenuated depression-like behavior in

adolescent mice and counteracted the spine abnormalities in the NAc induced by ELS. Additionally, SNS increased NAc Rac1 activity, and the inhibition of Rac1 activity weakened the antidepressant effect of SNS.

Conclusion: These results suggest that SNS may exert its antidepressant effects by modulating Rac1 activity and associated spine plasticity in the NAc.

KEYWORDS

early life stress, nucleus accumbens, adolescent depression, spine plasticity, Si-Ni-San



GRAPHICAL ABSTRACT

1 Introduction

Early Life Stress (ELS) primarily refers to stress experienced from the fetal stage through to puberty. This includes events such as early postnatal mother-infant separation, social isolation in early life, childhood abuse, trauma, neglect, and peer bullying (LeMoult et al., 2020; Zhao et al., 2022). ELS may alter the neural network of the emotional and cognitive systems, making adolescents more prone to the development of psychological and mental disorders (LeMoult et al., 2020). Although most mental disorders typically originate in adolescence, previous studies have largely focused on the impacts of early life stress on adults. Research examining the relationship between early life stress and adolescent depression is only just beginning (LeMoult et al., 2020). Therefore, it is crucial to investigate the mechanisms underlying ELS-induced depression during adolescence.

The primary symptom of adolescent depression is a loss of pleasure, which is tightly linked to dysfunction in the brain's reward circuit. The Nucleus Accumbens (NAc) serves as the hub for the interaction between dopamine, serotonin, and glutamate, playing a central role in mood and sensory regulation (Zhao et al., 2019). Recent research has demonstrated that early life stress significantly alters the transcription pattern in the NAc, thereby increasing the risk of depression (Pena et al., 2019; Hanson et al., 2021). In addition, it was reported that ELS decreased the response of NAc to rewards in adolescents (Lee et al., 2020). In recent years, synaptic structural remodeling of NAc neurons has been shown to play a critical role in depression. The primary neurons in the NAc (90%–95%) are medium spiny neurons (MSNs), which are projection neurons with numerous dendritic branches and a large number of dendritic spines on the dendrites (Golden et al., 2013; Hanson et al., 2021; Ru et al., 2022). Dendritic spines are tiny protrusions on neuron dendrites and are essential part of excitatory synapses. The structural remodeling of dendritic spines typically includes: 1) changes in spine density; 2) alterations in the shape of spines. Based on their morphology, dendritic spines are primarily divided into three types: stubby spines, thin spines, and mushroom dendritic spines. The size and shape of dendritic spines are closely associated with synaptogenesis and synaptic functional plasticity; as dendritic spines mature from immature (thin and stubby) to mature (mushroom), synaptic strength and stability are enhanced (Golden et al., 2013; Zhao et al., 2019). It has been reported that chronic social defeat stress notably increases the density of stubby spines in NAc MSNs. Alleviating the increase in stubby spine density can improve social avoidance behavior (Gebara et al., 2021), suggesting a close relationship between NAc spine remodeling and depression-like behavior. Despite

the importance of NAc spine remodeling in regulating depressive behavior, the impact of early life stress on spine remodeling of NAc in adolescent depression remains unclear.

RAS-related C3 Botulinum Toxin Substrate 1 (Rac1), a key member of the Rho family of small G proteins, plays a significant role in learning and memory, neuropsychiatric disorders, and neuronal synaptic plasticity (Zhao et al., 2019). It has been shown that chronic social stress triggers a reduction in NAc Rac1 expression and that a decrease in Rac1 activity contributes to depression-like behavior and mediates the increase of stubby spines in the NAc (Golden et al., 2013). Our previous studies also discovered that decreased Rac1 activity promoted methamphetamine addiction and increased the density of thin spines in the NAc (Tu et al., 2019; Zhao et al., 2019). However, the role of Rac1 in spine remodeling induced by early life stress remains unknown.

Si-Ni-San (SNS), a formula from the *Shang Han Lun* (Treatise on Febrile Diseases), is a commonly used basic formula in clinical treatment of depression. This formula is composed of four herbs, namely, Chaihu (*Radix Bupleuri*), Baishao (*Radix Paeoniae Alba*), Zhishi (*Fructus Aurantii Immaturus*), and roasted Gancao (*Radix Glycyrrhizae*) (Deng et al., 2022). An advanced study employing Ultrahigh-performance liquid chromatography-high-resolution tandem mass spectrometry (UPLC-HRMS/MS) revealed 713 compounds present in SNS. Remarkably, 13 of these compounds were determined to possess antidepressant properties. These compounds include Trigonelline, Formononetin, Stearic acid, Erucamide, Adenosine, Catechin, Hesperidin, Oleamide, Rutin, Naringin, Vitexin, L-Tyrosine, and Apigenin (Zhang et al., 2023). Additionally, another research identified 37 primary compounds in SNS, with prominent compounds like hesperidin, isoglycyrrhizin, glycyrrhizin, paeoniflorin, and saikosaponin A (Tian et al., 2021), which were also reported to have antidepressant-like effects (Wang et al., 2019; Dai et al., 2022). In addition, a substantial body of research on animals suggests that SNS has antidepressant effect, which can be contributed through the overall regulation of hypothalamus-pituitary adrenocortical system, monoamine neurotransmitters, brain-derived neurotrophic factor and synaptic plasticity (Shen et al., 2020; Wang et al., 2020; Deng et al., 2022). However, most studies have focused on adult depression, and few studies have explored the mechanisms involving the NAc in adolescents (Wang et al., 2020). Targeting synaptic structural plasticity within the NAc could potentially offer new avenues for the treatment of depression, particularly during the critical period of adolescence when the brain is highly malleable. Therefore, it is essential to further investigate the effects of SNS on depression in adolescents and the potential mechanisms regulating NAc spine plasticity in adolescent depression.

The main objective of this study is to examine the therapeutic potential and modulatory mechanisms of SNS in reversing abnormal behaviors and NAc spine plasticity induced by ELS. We hypothesize that SNS may influence depressive behaviors in adolescents exposed to ELS by potentially modulating Rac1 activity and associated dendritic spine dynamics in the NAc. This research holds the potential to elucidate new treatment strategies for adolescent depression, particularly interventions leveraging traditional Chinese medicine.

2 Materials and methods

2.1 Animals

C57BL/6 pregnant mice, purchased from Southern Medical University (Guangzhou, China) were maintained on a 12-h light/dark cycle with a constant temperature (22°C–24°C). The experiment was conducted in compliance with the Guide for the Care and Use of Laboratory Animals and was approved by the Animal Ethics Committee of Guangzhou University of Chinese Medicine, China (approval No. 2021W0050).

2.2 Early life stress paradigm

To assess the impact of ELS on adolescent depression, we utilized an animal model characterized by maternal separation and early weaning at postnatal day 17 (PND17), as established in previous research (Tchenio et al., 2017). Male C57/BL6 mouse pups were arbitrarily divided into two groups: those in the control group and those subjected to early life stress. The early life stress group was subjected to maternal separation from postnatal days 7–15 (PND7-15) and isolated in a new cage equipped with adequate bedding, water, and food for a duration of 6 h per day, with weaning initiated at PND17. Male pups from this group were randomly selected to constitute the ELS group on postnatal day 21 (PND21). On the other hand, the control group pups were left undisturbed until their regular weaning on PND21, after which male pups were randomly assigned to the control group.

2.3 Drug preparation and administration

The preparation method and doses calculating are based on our previous (Cao et al., 2019; Deng et al., 2022). SNS, derived from the *Shang Han Lun*, consists of Chai Hu, Shao Yao, Zhi Shi, and roasted Gan Cao in a 1:1:1:1 ratio. Each herb contributes 6 g to the formula. Both the herbal ingredients and fluoxetine procured from the First Affiliated Hospital of Guangzhou University of Chinese Medicine. The preparation of SNS followed traditional modern clinical practices. The herbs were weighed in equal proportions (1:1:1:1 ratio) and were then coarsely ground. The ground herbs were soaked in distilled water at ten times their weight for 60 min. After bringing the solution to a boil, it was simmered for 40 min. The solution was then allowed to cool and was subsequently filtered through an 8-layer cheesecloth to obtain the filtrate. The process was repeated: the herbs were boiled in 8 times the amount of water, simmered, cooled, and filtered. The filtrates from both rounds were combined. This combined solution was concentrated using a rotary evaporator to achieve a concentration of 1.96 g/mL of the original herb. The solution was then aliquoted and stored at 4°C for further use. Considering an average adult body weight of 60 kg/day for dose conversion, the clinically equivalent dose for mice was determined to be 4.9 g/kg. Using a 1:2:4 scaling, the low, medium, and high doses were set at 4.9 g/kg, 9.8 g/kg, and 19.6 g/kg, respectively. The quality and consistency of the SNS preparation were validated using high performance liquid chromatography (HPLC) according to our previous study (Deng et al., 2022). Fluoxetine, SNS and saline (as

a vehicle control) were administered via intragastric route from PND22 to PND42. Following the completion of this treatment, behavioral tests were conducted.

2.4 High performance liquid chromatography (HPLC)

For liquid chromatographic analysis, 1 mL of SNS solution (1.96 g/mL) was mixed with 23 mL of methanol. The mixture was subjected to ultrasonic radiation for 30 min to ensure uniform dissolution. Subsequently, it was filtered using a 0.45 μm microporous membrane to obtain a clear supernatant. Reference standards were prepared for the following compounds: Hesperidin (B20182, Shanghai Yuanye Bio-Technology Co., Ltd., China), Liquiritin (B20414, Shanghai Yuanye Bio-Technology Co., Ltd., China), Glycyrrhizic acid ammonium salt (IG0740, Beijing Solarbio Science and Technology Co., Ltd., China), Gallic acid (B20851, Shanghai Yuanye Bio-Technology Co., Ltd., China), Paeoniflorin (B21148, Shanghai Yuanye Bio-Technology Co., Ltd., China), Neohesperidin (B21390, Shanghai Yuanye Bio-Technology Co., Ltd., China). Each of these compounds was accurately weighed, dissolved in methanol, and then transferred to individual 1 mL volumetric flasks.

The analysis was performed on an Agilent HPLC-1200 System, utilizing a Diamonsil C18 (2) column (150 × 4.6 mm, 5 μm) maintained at 25°C. The mobile phase comprised of Solution A (acetonitrile) and Solution B (0.01 mol/L aqueous phosphoric acid). The solvent gradients were as follows: 0–10 min: 2%–10% A; 10–20 min: 10%–22% A; 20–28 min: 22%–29% A; 28–40 min: 29%–40% A; 40–50 min: 40%–55% A. Throughout the analysis, the flow rate was consistently maintained at 1 mL/min, and each injection had a volume of 10 μL.

2.5 Anxiety-like and depression-like behavior test

Anxiety-like behavior were assessed by open field test (OFT) and the elevated plus maze (EPM), while depression-like behaviors were measured using the sucrose preference test (SPT), the tail suspension test (TST), and the forced swim test (FST) according to our previous study (Zhao et al., 2023). OFT: Each mouse is placed at the center of an open field in a dimly lit room, and their movements are recorded for 10 min using a video camera. This test primarily evaluates the reluctance of the rodent to explore open spaces, which can be indicative of anxiety-like behavior. EPM: This test involves a cross-shaped elevated platform with two open arms and two closed arms. Animals are placed at the center, facing the open-arm direction. Their movement is recorded for 6 min in a dimly lit setting. SPT: To assess anhedonia, a hallmark symptom of depression, mice are initially habituated with two bottles containing a 1% sucrose solution for 2 days. On the third day (test day), they are presented with two bottles-one with 1% sucrose and the other with water-for 24 h. The sucrose preference is calculated as the ratio of the volume of sucrose solution consumed to the total liquid intake (sucrose + water) during the test day, expressed as a percentage. TST: Mice are suspended by the tail using tape, approximately 1 cm from the tail's tip and 25 cm off the ground. The amount of time the mouse remains immobile over a 6-min period is recorded. FST: Mice are placed in a cylindrical container filled with 25°C water up to a depth of 25 cm. After an initial 6-min period, the duration of immobility is recorded for the subsequent 4 min.

2.6 Viral constructs and microinjections

Lentiviruses expressing constitutively active Rac1 driven by the CMV promoter with a double-floxed inverted open reading frame combined with eGFP (DIO-Rac1-CA) and dominant negative Rac1 (DIO-Rac1-DN), or control lentivirus-eGFP (DIO-eGFP) were constructed by Obio Technology Corp., Ltd. Recombinant adeno-associated virus serotype 2/9 (AAV 2/9) expressing mCherry in combination with the Cre enzyme driven by the CMV promoter (CMV-Cre), lentivirus-eGFP (LV-eGFP), and rAAV-hSyn-eGFP-WPRE were constructed by Obio Technology Corp., Ltd. CMV-Cre and DIO-Rac1-CA, DIO-Rac1-DN or DIO-eGFP were bilaterally infused into the NAc over 5 min (coordinates AP, +1.54 mm; ML, ±0.80 mm; and DV,−4.20 mm) according to our previous studies (Tu et al., 2019; Zhao et al., 2019; Ying et al., 2022). Upon Cre-mediated recombination of the DIO, eGFP, Rac1-CA or Rac1-DN are expressed. Rac1-CA simulates the activated state of the wild-type G-protein by mutating glutamine 61 of Rac1 to leucine (Zhang et al., 2006). Rac1-DN inhibits the activity of Rac1 by mutating threonine 17 of Rac1 to asparagine (Tong et al., 2013). In our earlier research, we've shown that Rac1-CA can effectively activate Rac1-GTP and its downstream effector, p-PAK, while Rac1-DN inhibits their activity (Zhao et al., 2019).

2.7 Dendritic spine analysis of the MSNs

To observe the impact of ELS on the NAc dendritic spines, the virus rAAV-hSyn-eGFP-WPRE was randomly infused into the NAc of both control and ELS mice at PND22. Three mice were used for each group. To investigate the effect of Rac1 on the NAc dendritic spines, the CMV-Cre and either DIO-Rac1-CA, DIO-Rac1-DN, or DIO-eGFP were randomly infused into the NAc of control and ELS mice. Subsequently, based on the type of viral injection, mice were grouped into control + eGFP, ELS + eGFP, control + Rac1-CA, ELS + Rac1-CA, control + Rac1-DN, and ELS + Rac1-DN. After ensuring full viral expression, all groups underwent behavioral tests. After the behavioral test, three mice were randomly selected from each group for dendritic spine analysis. Furthermore, to assess the influence of Si-Ni-San on dendritic spines, three mice were randomly chosen from the control, ELS, positive, and SNS medium dose groups at PND22. The virus rAAV-hSyn-eGFP-WPRE was randomly infused into the NAc of selected mice. Following the behavioral experiments, dendritic spine analysis was conducted. Dendritic spine analysis were performed according to our previous studies (Tu et al., 2019; Zhao et al., 2019; Zhao et al., 2022). The primary antibody was anti-GFP antibody (1:500, Abcam). The second antibody was Alexa Fluor 488-conjugated anti-rabbit antibody (1:200, Invitrogen).

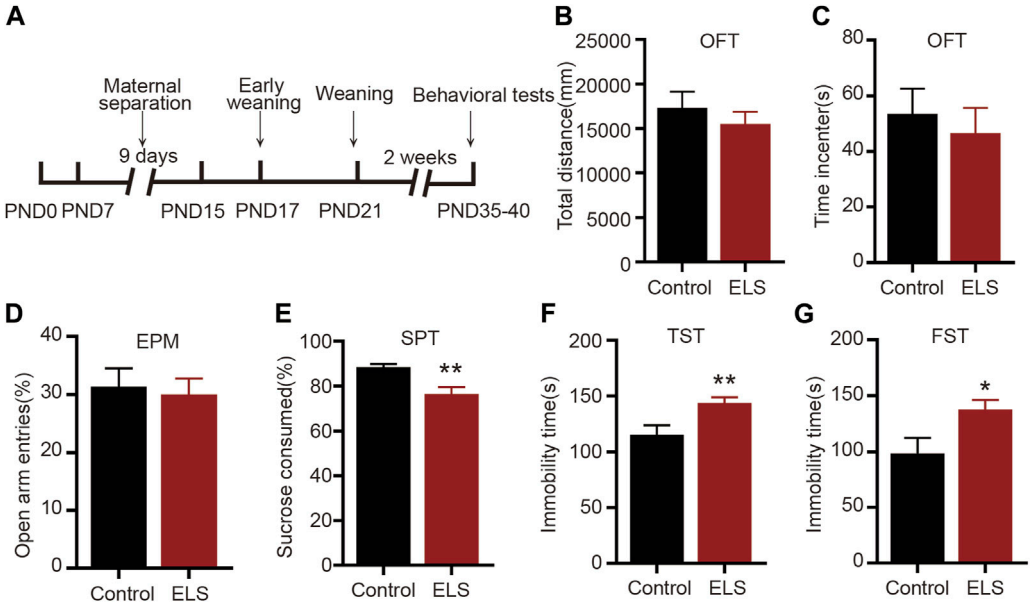


FIGURE 1
Early life stress induced depression-like, not anxiety-like behaviors, in adolescent mice: **(A)** An experimental paradigm for early life stress. **(B,C)** There was no significant change in the total distance and time spent in the center in the open field test between the two groups (n = 14 mice per group). **(D)** In comparison to the control group, there was no significant change in the percentage of open arm entries in the ELS group (n = 14 mice per group). **(E)** The percentage of sucrose consumed of the ELS group was significantly decreased (n = 14 mice per group). **(F)** Compared with the control group, the immobility time was significantly increased in the ELS group in the tail suspension test (n = 14 mice per group). **(G)** Compared with the control group, the immobility time in the forced swimming test was significantly increased in the ELS group (n = 14 mice per group). Data were analyzed using Student's t-test presented as mean ± SEM. $^{**}p < 0.01$ and $^{*}p < 0.05$ compared to the control group.

2.8 Rac1 activity assay and western blots analysis

The pull-down assay and Western blotting were performed were performed as described before (Zhao et al., 2019). The primary antibodies included the following: anti-Rac1 (1:1000, BD Transduction Laboratories); p-Pak and Pak (1:1000, Cell Signaling); Peroxidase-conjugated goat anti-rabbit or anti-mouse IgG second antibodies (1:5000, Santa Cruz Biotechnology Inc.).

2.9 Statistical analysis

Statistical analysis was conducted using SPSS 20.0 software. One-way or two-way ANOVA followed by Bonferroni's *post hoc* test were employed to evaluate differences among multiple groups, while two groups were performed using Student's t-tests. Significance was set at $p < 0.05$. Details were described in Supplementary Material.

3 Results

3.1 Early life stress induced depression-like, not anxiety-like behaviors, in adolescent mice

We first evaluated whether early life stress induced depression-like or anxiety-like behavior in adolescent mice. The early-life stress protocol is illustrated in Figure 1A. The OFT and EPM are used to evaluate anxiety-like behavior in adolescent mice. When compared with the control group, the ELS group did not display a significant difference in terms of total distance traversed (Figure 1B, n = 14, p = 0.427) or time spent in the center during the OFT (Figure 1C, n = 14, p = 0.591). Similarly, there was no significant difference in the percentage of open arm entries in the ELS group in EPM (Figure 1D, n = 14, p = 0.761). The FST and TST was used to assess behavioral despair and SPT was used to measure anhedonia-like phenotypes in depression-related behavior. As shown in Figure 1E, the ELS group showed a considerable reduction in the percentage of sucrose intake (Figure 1E, n = 14, p = 0.001). Additionally, an increase in immobility time was observed in the tail suspension test (Figure 1F, n = 14, p = 0.007) and the forced swimming test (Figure 1G, n = 14, p = 0.011) for the ELS group. Taken together, these findings suggest that early life stress primarily induced depression-like, not anxiety-like behaviors, in adolescent mice.

3.2 Early life stress induced spine remodeling in the NAc of adolescent mice

Chronic stress is known to elicit structural remodeling of dendritic spines. Such alterations can influence the strength and number of synaptic connections between neurons, thereby affecting neural circuits related to mood and emotion regulation (Gebara et al., 2021). To further explore the impact of ELS on the NAc dendritic spines, the virus rAAV-hSyn-eGFP-WPRE was randomly

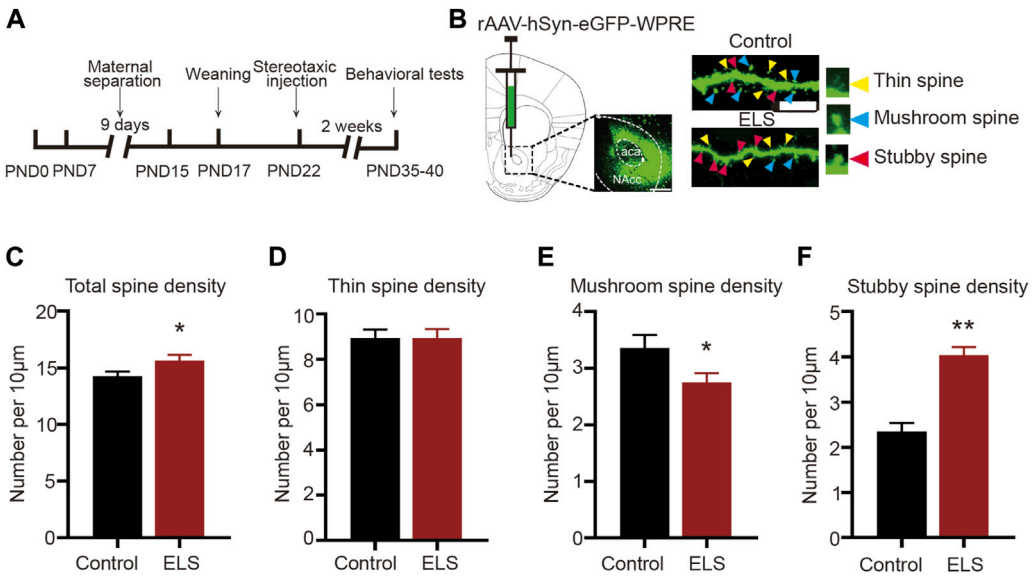


FIGURE 2
Early life stress induced spine remodeling in the NAc of adolescent mice: **(A)** Anatomical location of the NAc injected with a lentivirus expressing eGFP. Scale bar = 500 μm. **(B)** Representative image of eGFP-labelled spines in the NAc. Scale bar = 10 μm. **(C)** Compared with the control group, the total spine density of the ELS group was significantly increased. **(D)** Compared with the control group, the thin spine density of the ELS group had no significant change. **(E)** Compared with the control group, the mushroom spine density of the ELS group was significantly decreased. **(F)** Compared with the control group, the stubby spine density of the ELS group was significantly increased. 8–12 dendrite sections per animal with 3 animals per group. Data were analyzed using Student's t-test presented as mean ± SEM. $^{**}p < 0.01$ and $^{*}p < 0.05$ compared to the control group.

infused into the NAc of both control and ELS mice at PND22. Figures 2A, B schematically represents the area of rAAV-hSyn-eGFP-WPRE injection and the image of eGFP-labelled spines in the NAc. Our findings revealed notable differences in spine morphology between the ELS group and controls. Specifically, compared to the control group, the total spine density was significantly increased in the NAc of ELS group (Figure 2C, 8–12 dendrite sections per animal with 3 animals per group, $p = 0.033$). While thin spine density did not show any significant difference between groups (Figure 2D, $p = 0.997$), we observed a marked decrease in mushroom spine density (Figure 2E, $p = 0.039$) and a substantial increase in stubby spine density (Figure 2F, $p < 0.001$) for the ELS group. These findings suggest that early life stress triggers a restructuring of dendritic spines within the NAc of adolescent mice.

3.3 Increased Rac1 activity in the NAc improved early life stress induced-depression-like behaviors

Rac1 plays a significant role in several psychiatric disorders, such as addiction and depressive disorder (Zhao et al., 2019; Ru et al., 2022). We further evaluated the role of Rac1 in ELS induced-depression-like behaviors. AS shown in Figures 3A–C, both Rac1-GTPase (Figure 3B, $n = 5$, $p = 0.033$) and its downstream p-PAK (Figure 3C, $n = 5$, $p = 0.011$) activities were decreased in the NAc of the ELS group compared to the control group. Then, to investigate whether the decrease of Rac1 mediated early life stress induced-depression-like behaviors, CMV-Cre and DIO-Rac1-CA, DIO-Rac1-DN or DIO -eGFP were bilaterally infused into the NAc. Upon Cre-mediated recombination of the DIO, eGFP, Rac1-CA or Rac1-DN are expressed (Figures 3D, E). As shown in Figures 3F, G the constructed Rac1 mutant viruses were able to regulate the activity of Rac1 (Figure 3F, $n = 4$, Rac1-CA vs. eGFP: $p = 0.043$; Rac1-DN vs. eGFP: $p = 0.01$) and its downstream p-Pak activity (Figure 3G, $n = 4$, Rac1-CA vs. eGFP: $p = 0.044$; Rac1-DN vs. eGFP: $p = 0.01$) in the NAc. Moreover, Rac1-CA reversed the low percentage of sucrose consumption observed in the ELS group (Figure 3H, $n = 8$, $p = 0.001$), while Rac1-DN induced a decrease in the percentage of sucrose consumed in the control group (Figure 3H, $p = 0.03$). Similarly, Rac1-CA reversed the increase in immobility time in the ELS group in the tail suspension (Figure 3I, $n = 8$, $p = 0.038$) and forced swimming tests (Figure 3J, $n = 8$, $p < 0.001$), while Rac1-DN induced an increase in immobility time in the control group (Figure 3I, $n = 8$, $p < 0.001$; Figure 3J, $n = 8$, $p = 0.002$). These findings suggest that Rac1 plays a significant role in regulating behaviors associated with depression that result from early life stress.

3.4 Increased Rac1 activity in the NAc improved early life stress induced-spine abnormalities in the NAc

Rac1 plays a significant role in spine plasticity (Zhao et al., 2019). Therefore, we further examined its role in the spine abnormalities in the NAc induced by ELS. Figure 4A depicted a representative image of the dendrites of neurons in the NAc. We discovered that the

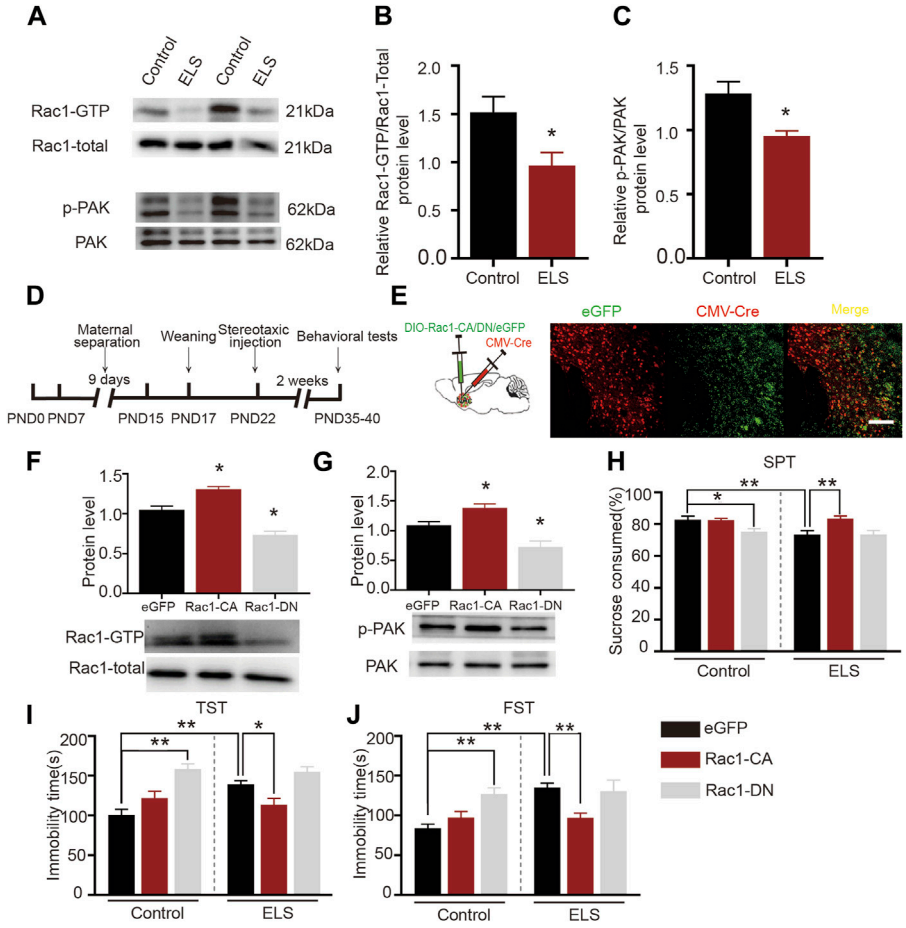


FIGURE 3
Increased Rac1 activity in the NAc improved early life stress induced-depression-like behaviors: **(A)** Representative band diagram of Rac1-GTP, Rac1-total, p-PAK, PAK protein in the NAc. **(B,C)** Both Rac1-GTPase and its downstream p-PAK activities were decreased in the NAc of the ELS group (n = 5 mice per group). **(D)** Diagram of brain area injection. **(E)** Representative images showing colocalization of CMV-Cre virus (red) and eGFP (green) in the NAc. Scale bar = 100 μm. **(F,G)** Western blots for Rac1 and p-Pak activity after the injection Rac1 mutant viruses (n = 4 mice per group). **(H)** The effects of Rac1 mutant viruses on the percentage of sucrose consumed (n = 8 mice per group). **(I)** The effects of Rac1 mutant viruses on the immobility time in tail suspension test (n = 8 mice per group). **(J)** The effects of Rac1 mutant viruses on the immobility time in forced swimming test (n = 8 mice per group). Data were analyzed using Student's t-test **(B,C)**, one-way **(F,G)** or two-way ANOVA **(H–J)** followed by Bonferroni's *post hoc* test and presented as mean ± SEM. $^{**}p < 0.01$ and $^{*}p < 0.05$.

overexpression of Rac1-CA significantly decreased the total spine density in the NAc that was induced by early life stress (Figure 4B, 8–12 dendrite sections per animal with 3 animals per group, p = 0.0.021), while the overexpression of Rac1-DN on its own resulted in a significant increase in total spine density, mirroring the effect of early life stress on spine remodeling in the NAc (Figure 4B, p = 0.009). As shown in Figure 4C, Rac1 did not affect the density of thin spines. Moreover, the reduction in mushroom spine density in the early life stress group was reversed by the Rac1-CA virus (Figure 4D, p = 0.001), and Rac1-DN was able to reduce mushroom spine density in the control group (Figure 4D, $p < 0.001$). Additionally, overexpression of Rac1-CA significantly decreased stubby spine density in the NAc induced by early life stress (Figure 4E, $p <$ 0.001), whereas the overexpression of Rac1-DN led to a significant increase in stubby spine density in the NAc compared to the control group (Figure 4E, $p < 0.001$). All these findings suggest that a decrease in Rac1 activity in the NAc plays an important role in spine remodeling in the NAc induced by ELS.

3.5 Administration of SNS improved depressive-like behavior and spine abnormalities in the NAc induced by early life stress

A substantial body of research on animals suggests that SNS and its modified prescriptions have an antidepressant effect, which may be attributed to the overall regulation of the hypothalamus-pituitary-adrenal system, monoamine neurotransmitters, brain-derived neurotrophic factor, and synaptic plasticity (Shen et al., 2020; Deng et al., 2022). However, the antidepressant mechanism of SNS is rarely designed for the spine remodeling in the NAc. Therefore, we further investigated whether SNS could alleviate ELS-induced depression-like behaviors and spine abnormalities in the NAc. As shown in Figure 5A, SNS was administered intragastrically at the dose of at 4.9 g/kg (low dose group), 9.8 g/kg (medium dose group), and 19.6 g/kg (high dose group). We found that SNS exerted a significant antidepressant effect. All

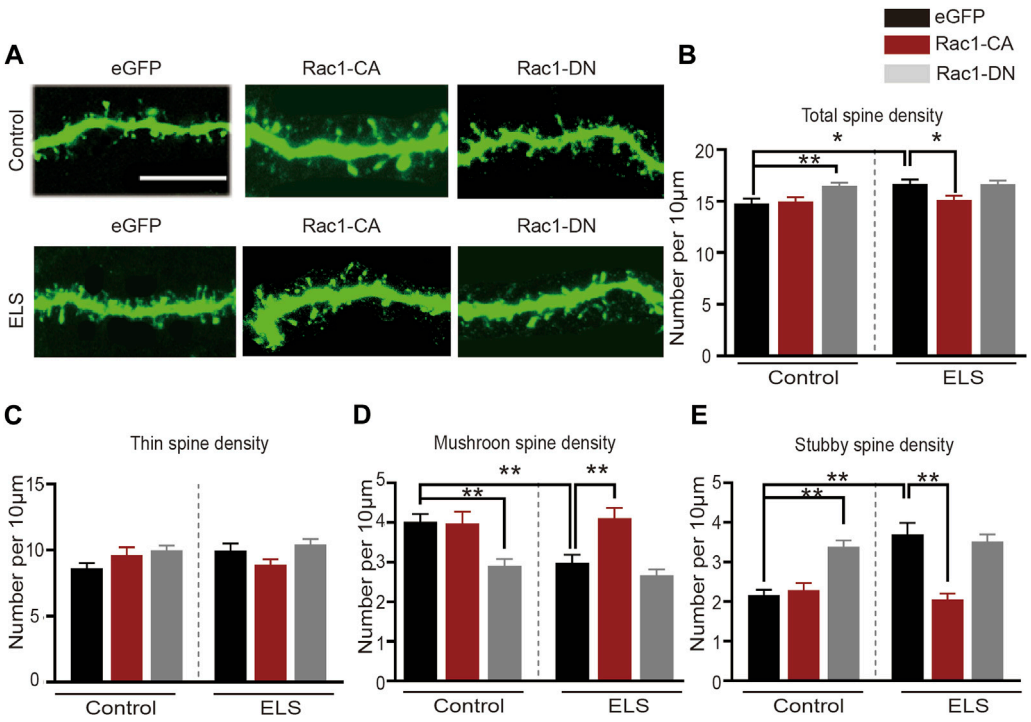


FIGURE 4
Increased Rac1 activity in the NAc improved early life stress induced-spine abnormalities in the NAc: **(A)** representative confocal images of GFP-labeled dendritic spines in the NAc. Scale bar = 10 μm. **(B)** The effects of Rac1 mutant virus on the total spine density in the NAc. **(C)** The effects of Rac1 mutant virus on thin spine density in NAc. **(D)** The effects of Rac1 mutant virus on the mushroom spine density in the NAc. **(E)** The effects of Rac1 mutant virus on the stubby spine density in the NAc. 8–12 dendrite sections per animal with 3 animals per group. Data were analyzed using two-way ANOVA followed by Bonferroni's *post hoc* test and presented as mean ± SEM. $^{**}p < 0.01$ and $^{*}p < 0.05$.

three doses of SNS significantly increased the percentage of consumed sucrose (Figure 5B, $n = 14$, ELS vs. Control: $p < 0.001$; Positive vs. ELS: $p < 0.001$; SNS-L vs. ELS: $p = 0.002$; SNS-M vs. ELS: $p = 0.001$, SNS-H vs. ELS: $p = 0.001$). Furthermore, all three doses of SNS decreased immobility time in both the tail suspension (Figure 5C, $n = 14$, ELS vs. Control: $p = 0.001$; Positive vs. ELS: $p = 0.002$; SNS-L vs. ELS: $p < 0.001$; SNS-M vs. ELS: $p = 0.008$; SNS-H vs. ELS: $p = 0.001$) and forced swimming experiments (Figure 5D, $n = 14$, ELS vs. Control: $p < 0.001$; Positive vs. ELS: $p = 0.007$; SNS-L vs. ELS: $p = 0.025$; SNS-M vs. ELS: $p = 0.009$; SNS-H vs. ELS: $p = 0.002$). These results suggest that SNS could improve adolescent depression-like behavior induced by ELS. We also evaluated whether SNS could ameliorate spine deficits in the NAc induced by early life stress. Figure 5E presents representative confocal images of dendritic spines in the NAc. We found that SNS reversed the increase in total spine density in the NAc induced by early life stress (Figure 5F, $n = 4$, ELS vs. Control: $p = 0.028$; Positive vs. ELS: $p = 0.007$; SNS vs. ELS: $p = 0.035$). Moreover, SNS had no effect on the density of thin spines in the NAc (Figure 5G, $n = 4$, ELS vs. Control: $p = 0.356$; Positive vs. ELS: $p = 0.131$; SNS vs. ELS:$p = 0.092$). Additionally, SNS administration significantly increased mushroom spine density (Figure 5H, $n = 4$, ELS vs. Control: $p = 0.006$; Positive vs. ELS: $p = 0.048$; SNS vs. ELS: $p = 0.014$) and decreased stubby spine density (Figure 5I, $n = 4$, ELS vs. Control: $p = 0.005$; Positive vs. ELS: $p < 0.001$; SNS vs. ELS: $p < 0.001$) in the NAc induced by ELS. These results indicate that SNS may alleviate depression-like behaviors in adolescence by modulating spine plasticity in the NAc.

3.6 The effects of Rac1 signalling on the antidepressant action of SNS in adolescence

Given the established association between Rac1 activity in the NAc and depression-like behaviors, as well as spine remodeling due to early life stress, we further investigated Rac1's involvement in the antidepressant effects of SNS. We initially measured the impact of SNS on Rac1 activity in the NAc. As demonstrated in Figure 6A, SNS significantly increased Rac1 (Figure 6B, $n = 4$, ELS vs. Control: $p = 0.004$; Positive vs. ELS: $p = 0.023$; SNS vs. ELS: $p = 0.016$) and its downstream p-PAK activity (Figure 6C, $n = 4$, ELS vs. Control: $p = 0.022$; Positive vs. ELS: $p = 0.035$; SNS vs. ELS: $p = 0.015$). Furthermore, we found that overexpression of Rac1-DN significantly weakened the antidepressant effect of SNS, as shown by the decrease in the percentage of consumed sucrose (Figure 6D, $n = 8$, ELS vs. Control: $p = 0.005$; SNS vs. ELS:$p = 0.007$; SNS vs. SNS-Rac1-DN: $p = 0.016$), and the increase in immobility time in both the tail suspension (Figure 6E, $n = 8$, ELS vs. Control: $p = 0.004$; SNS vs. ELS: $p < 0.001$; SNS vs. SNS-Rac1-DN: $p = 0.018$) and forced swimming tests (Figure 6F, $n = 8$, ELS vs. Control: $p = 0.005$; SNS vs. ELS: $p = 0.011$; SNS vs. SNS-Rac1-DN: $p = 0.038$). These

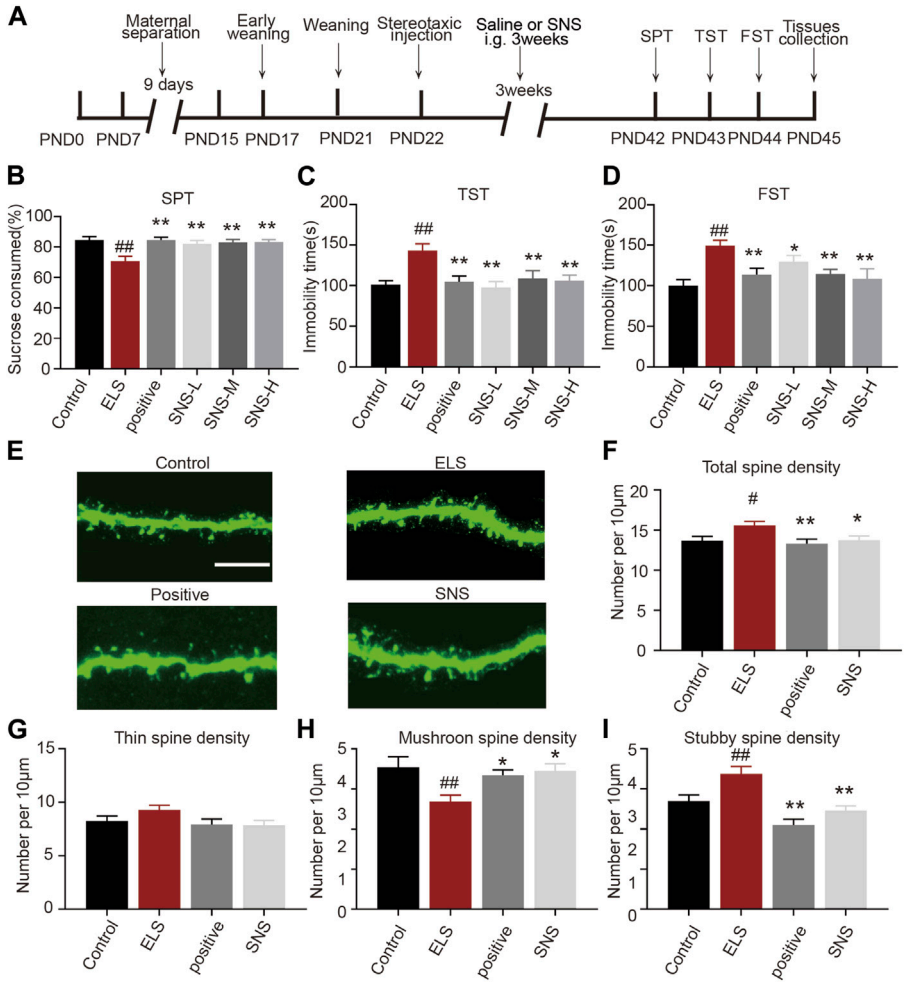


FIGURE 5
Administration of SNS improved depressive-like behavior and spine abnormalities in the NAc induced by early life stress: **(A)** Schematic diagram of the experimental flow. **(B)** The effects of SNS on the percentage of sucrose consumed (n = 14 mice per group). **(C)** The effects of SNS on the immobility time in tail suspension test (n = 14 mice per group). **(D)** The effects of SNS on the immobility time in forced swimming test (n = 14 mice per group). **(E)** Representative confocal images of GFP-labeled dendritic spines in the NAc. Scale bar = 10 μm. **(F)** The effects of SNS on the total spine density in the NAc. **(G)** The effects of SNS on the thin spines density in the NAc. **(H)** The effects of SNS on the mushroom spine density in the NAc. **(I)** The effects of SNS on the stubby spine density in the NAc. 8–12 dendrite sections per animal with 3 animals per group. Data were analyzed using one-way ANOVA followed by Bonferroni's *post hoc* test and presented as mean ± SEM. ##$p < 0.01$ and #$p < 0.05$ compared to the control group, **$p < 0.01$ and *$p < 0.05$ compared to the ELS group.

results suggest that the antidepressant action of SNS is mediated, at least in part, by modulating Rac1 activity within the NAc.

4 Discussion

In this study, our findings revealed that ELS significantly induced depression-like behaviors in adolescent mice. Additionally, ELS increased the stubby spine density while decreasing mushroom spine density in the NAc. Furthermore, ELS reduced Rac1 activity in the NAc, and the overexpression of a constitutively active Rac1 in the NAc reversed depression-related behaviors and led to a decrease in stubby spine density and an increase in mushroom spine density, suggesting that Rac1 plays a crucial role in the behavioral and spine abnormalities induced by ELS during adolescence. Moreover, SNS mitigated depression-like behavior in adolescent mice and counteracted the spine abnormalities in the NAc induced by ELS. Additionally, SNS increased NAc Rac1 activity, and the overexpression of a dominant-negative Rac1 weakened the antidepressant effect of SNS. Our results suggest that SNS may exert its antidepressant effects by modulating Rac1 activity and associated spine plasticity in the NAc.

Maternal separation, social isolation, and other forms of ELS significantly increase risk for depression. Previous studies have largely focused on the impacts of ELS on adults (Hanson et al., 2021; Waters and Gould, 2022). For instance, ELS from PND10–20 changed transcriptomic patterning in the brain's reward circuitry and increased the susceptibility to depression-like behavior in adult mice (Pena et al., 2019). In our study, we used an ELS animal model of maternal separation with early weaning to evaluate the effects of ELS on behavioral

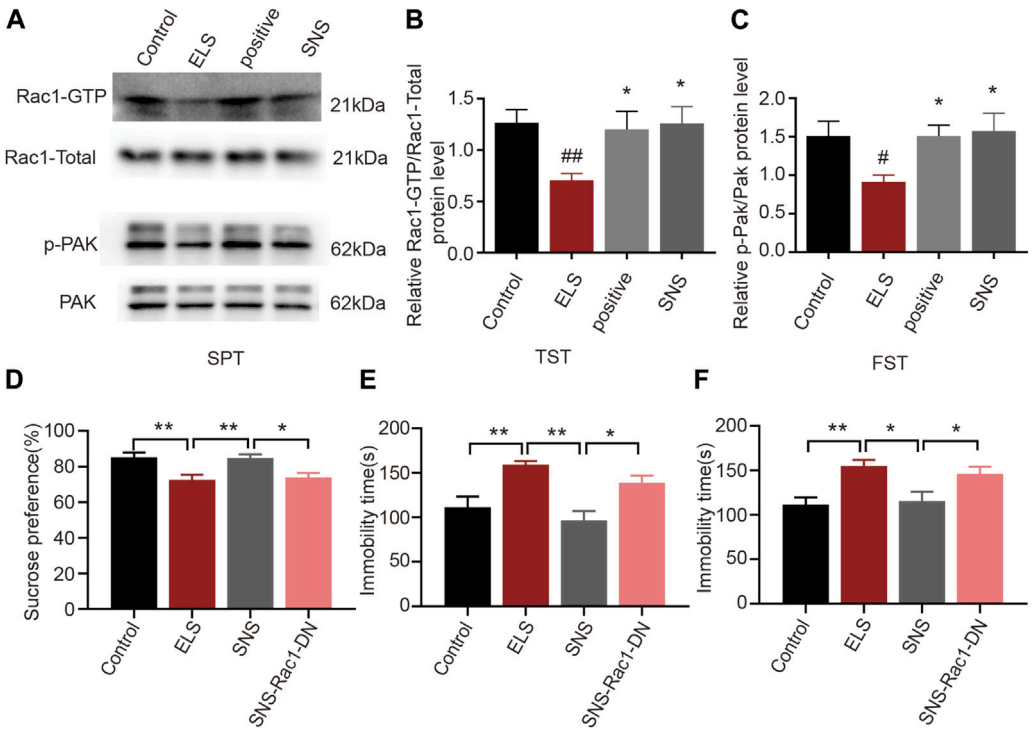


FIGURE 6
The effects of Rac1 signalling on the antidepressant action of SNS in adolescence: **(A)** Representative band diagram of Rac1-GTP, Rac1-total, p-PAK, PAK protein in the NAc. **(B,C)** Effects of SNS on the Rac1 and p-PAK activity in the NAc (n = 4 mice per group). **(D)** Rac1-DN weakened the antidepressant effect of SNS on the percent of sucrose consumed in sucrose preference test (n = 8 mice per group). **(E)** Rac1-DN weakened the antidepressant effect of SNS on the immobility time in tail suspension test after SNS administration (n = 8 mice per group). **(F)** Rac1-DN weakened the antidepressant effect of SNS on the immobility time in forced swimming test (n = 8 mice per group). Data were analyzed using one-way ANOVA followed by Bonferroni's *post hoc* test and presented as mean ± SEM. $^{**}p < 0.01$ and $^{*}p < 0.05$.

abnormalities in adolescence. The ELS paradigm was based on both rodent maternal separation studies and work demonstrating early weaning reduced compensatory maternal care after maternal separation (Tchenio et al., 2017; Waters and Gould, 2022). In this study, we found that ELS induced depression-like behavior in adolescence which is in accordance with previous study (Tchenio et al., 2017; Alteba et al., 2021; Chen et al., 2021). A study has shown that maternal separation combined with early weaning induced anxiety-like behavior in rats (Zeng et al., 2020). The discrepancy between their findings and ours might arise from species differences. This speculation is substantiated by research indicating that the effects of early life stress on depression and anxiety-like behaviors can be both species and gender-specific (Zeng et al., 2021). Another study reported that maternal separation with early weaning induced anxiety, hyperactivity, and behavioral despair in CD1 mice (Gracia-Rubio et al., 2016). Importantly, it is noteworthy that many experiments involving C57BL/6J male mice have yielded divergent outcomes concerning depression and anxiety-like behaviors (Tan et al., 2017). The manifestation of depression-like behaviors without concurrent anxiety-like behaviors in our study might be attributed to variances in the maternal separation protocol. Indeed, research has shown that the consequences of the maternal separation protocol depend on the duration, developmental stage, and number of days of the separation experience (Nishi, 2020).

NAc is a key brain region involved in reward processing and motivation. It plays a crucial role in the development of depressive symptoms (Golden et al., 2013; Zhao et al., 2022). A recent study suggested that ELS induced enduring transcriptional changes in the NAc that may underlie vulnerability to stress in adulthood (Pena et al., 2019). Previous studies investigating the relationship between spine plasticity and stress have been conducted in the context of social stress, but not in the context of early life stress (Warren et al., 2014; Lee et al., 2020). It is not yet known how ELS alters NAc spine plasticity in adolescence. In this study, we found that ELS increased total density of dendritic spines, especially those of stubby spines of the NAc in male mice. Additionally, ELS decreased mushroom spine density in the NAc. Our study was consistent with previous study demonstrating that emotional stress and physical stress increased spine density in the NAc of adolescent exposed mice (Warren et al., 2014). Similarly, it was reported that high-trait-anxiety rats showed more thin spines and fewer mushroom spines in the NAc (Gebara et al., 2021). Our previous study also demonstrated that adolescent social isolation induced anxiety-like behavior and increased thin spine density in the NAc (Zhao et al., 2022). To our knowledge, this study is the first to evaluate the effect of ELS on spine plasticity in the NAc during adolescence. Spine remodeling provides the structural basis for functional changes in neural circuits. Stubby spines are relatively short and are thought to represent newly formed or less stable synapses, and they are more dynamic and can undergo changes in density and shape. Mushroom spines are considered mature and stable, representing well-established and strong synapses, and are associated with long-term synaptic potentiation

(Runge et al., 2020; Zhao et al., 2022). Previous study also reported that chronic social defeat stress notably increases the density of stubby spines in NAc MSNs (Golden et al., 2013). In addition, it was reported that increased spine density was associated with hyperexcitability of neurons (Ru et al., 2022). Thus, we speculate that increased stubby spine density and decreased mushroom spine density in the NAc may reflect heightened sensitivity to stress in adolescence. A recent study also demonstrated that adolescents with major depressive disorder showed increased NAc volume, which was significantly correlated with depressive symptoms in adolescence (Lee et al., 2020). In addition, it was reported that dendritic spine density was associated with brain volumetric changes (Keifer et al., 2015). Taken together, these findings indicate that NAc spine density may be one possible structural alteration that plays an important role in adolescent depression.

Rac1 is a small GTPase protein that plays a crucial role in regulating actin cytoskeleton dynamics and cellular processes such as spine, and synapse development. Over time, evidence has suggested that Rac1 plays a significant role in several psychiatric disorders, such as addiction and depressive disorder (Zhao et al., 2019; Ru et al., 2022). However, the protective role of Rac1 has not yet been examined in an animal model of adolescent depression. Our results showed that maternal separation combined with early weaning could decrease Rac1 activity, whereas increased Rac1 activity could improve depressive-like behavior and prevent spine abnormalities in the NAc caused by early life stress. This is consistent with our previous studies demonstrating that Rac1 attenuated behavioral and spine abnormalities in the NAc induced by methamphetamine (Zhao et al., 2019). Additionally, it is worth noting that previous evidence from the social defeat mice model showed that malvidin-3′-O-glucoside exerts an antidepressant effect by enhancing Rac1 expression in the NAc (Wang et al., 2018). Taken together, our evidence further supports the important role of rac1 in spine remodeling and the treatment of depression, especially in adolescent depressive patients who have experienced early life stress.

SNS was first documented in Zhang Zhongjing's Treatise on Febrile Diseases. It has been traditionally considered a classic formula for soothing the liver and alleviating depression, and showed many advantages in the treatment of depression (Deng et al., 2022). Our previous studies have demonstrated that SNS delivers anti-depressive effects by regulating hippocampal synaptic plasticity, mitochondrial function, and brain-derived neurotrophic factor content in a rat depression model (Cao et al., 2019; Shen et al., 2020; Deng et al., 2022). Recent investigations also revealed that SNS could produce antidepressant effects by regulating the biosynthesis and metabolism of steroid hormones in the liver (Wang et al., 2020). However, the impact of SNS on adolescent depression and the potential mechanisms governing NAc spine plasticity in such cases had not been examined prior to this study. Our findings indicated that SNS improved depression-like behavior in adolescent mice, reversing the spine abnormalities in the NAc induced by ELS. Additionally, SNS enhanced Rac1 activity, and the inhibition of Rac1 activity weakened the antidepressant effect of SNS. This evidence suggests that SNS executes its antidepressant action by modulating NAc spine remodeling through Rac1. A recent study also demonstrated that the antidepressant effects of SNS were associated with anti-inflammatory benefits (Zong et al., 2019). Moreover, SNS ameliorated depression-like behavior induced by chronic unpredictable mild stress by regulating dendritic spines in the hippocampus via NCOA4-mediated ferritinophagy (Zhang et al., 2023). It is important to note that most studies concerning the antidepressant effect of SNS have been primarily focused on the hippocampus (Zong et al., 2019; Deng et al., 2022; Zhang et al., 2023), and no articles have evaluated the role of the NAc in SNS's antidepressant effect. To the best of our knowledge, our study is the first to report that Rac1-mediated spine remodeling of NAc plays a crucial role in the antidepressant effect of SNS. However, our study does come with certain limitations. For instance, while numerous studies have underscored the antidepressant-like effects of primary SNS components, including hesperidin, isoglycyrrhizin, glycyrrhizin, paeoniflorin, and saikosaponin A, our investigation did not extensively explore these specific therapeutic constituents in the context of ELS-induced depression. Furthermore, while we have established a connection between Rac1 activity and the observed behavioral and spine anomalies induced by ELS, the extensive role of Rac1 and its interactions with other variables remain to be elucidated. Further investigations are required to explore the depth of the relationship between Rac1 activity, spine abnormalities, and behavioral changes induced by ELS. Additionally, a comprehensive exploration of the distinct therapeutic constituents of SNS and their individual and collective influences on depression-like behaviors is warranted.

In summary, our results provide strong evidence that Rac1 is a critical factor in the pathophysiology of ELS-induced depressive-like behavior in adolescence and SNS exerts its antidepressant action by modulating Rac1 activity and associated spine plasticity in the NAc. This research not only advances understanding of the neurobiological mechanisms underpinning depression induced by early life stress, but also provides evidence for the integration of traditional Chinese medicine into therapeutic approaches.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

The animal study was approved by the Experimental Animal Care and Use Committee at Guangzhou University of Chinese Medicine. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

LiY: Writing–original draft, Formal Analysis, Methodology. JW: Formal Analysis, Resources, Writing–review and editing. ZuL: Formal Analysis, Resources, Writing–review and editing. DD: Resources, Writing–review and editing. SB: Resources, Writing–review and editing. LeY: Resources, Writing–review and editing. YX: Writing–review and editing, Formal Analysis. ZeL:

Formal Analysis, Writing–review and editing. YS: Writing–review and editing, Validation. ZhL: Writing–review and editing, Resources. RZ: Resources, Project administration, Writing–original draft. JZ: Project administration, Resources, Writing–original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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EDITED BY
Magdalena Sowa-Kucma,
University of Rzeszow, Poland

REVIEWED BY
Tomasz Boczek,
Medical University of Lodz, Poland
Maria Bogdan,
University of Medicine and Pharmacy of Craiova, Romania

*CORRESPONDENCE
Jing Teng,
60170099@sdutcm.edu.cn

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Antidepressant pharmacological mechanisms: focusing on the regulation of autophagy

Shimeng Lv[1], Guangheng Zhang[1], Yufei Huang[2], Jiamin Li[1], Ni Yang[1], Yitong Lu[1], Haoteng Ma[3], Yuexiang Ma[3] and Jing Teng[1]*

[1]Department of First Clinical Medical College, Shandong University of Traditional Chinese Medicine, Jinan, China, [2]Ruijin Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China, [3]College of Traditional Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan, China

The core symptoms of depression are anhedonia and persistent hopelessness. Selective serotonin reuptake inhibitors (SSRIs) and their related medications are commonly used for clinical treatment, despite their significant adverse effects. Traditional Chinese medicine with its multiple targets, channels, and compounds, exhibit immense potential in treating depression. Autophagy, a vital process in depression pathology, has emerged as a promising target for intervention. This review summarized the pharmacological mechanisms of antidepressants by regulating autophagy. We presented insights from recent studies, discussed current research limitations, and proposed new strategies for basic research and their clinical application in depression.

KEYWORDS

depression, autophagy, Traditional Chinese medicine, pharmacological mechanisms, antidepressant

1 Introduction

Major depressive disorder (MDD), also known as depression, is a mood disorder characterized by enduring feelings of sadness and anhedonia. It is a significant contributor to global suicide rates. According to the World Health Organization, depression affects approximately 4.4% of the global population, exceeding 350 million individuals. By 2030, depression is projected to become the leading cause of global burden of disease and non-fatal health-related losses (Rehm and Shield, 2019; Bayes et al., 2020). Treatment of depression primarily involves the use of selective serotonin reuptake inhibitors (SSRIs) and related medications. SSRIs exert their pharmacological action by selectively inhibiting serotonin (5-HT) transporters, prolonging and enhancing the effects of 5-HT, thereby exhibiting antidepressant properties (Perez-Caballero et al., 2014; Bi et al., 2022). However, SSRIs have adverse reactions such as nausea, headache, chronic sexual dysfunction, and weight gain (Wang et al., 2019a). Furthermore, they often have delayed onset and high non-response rates (Qu et al., 2021; Wei et al., 2022). Therefore, there is a need for safer and more effective antidepressants. Traditional Chinese medicine (TCM) offers promise due to its diverse components, targets, and modes of action. Moreover, it has been demonstrated that the active components and compounds found in TCM have shown notable effectiveness in treating depression with minimal side effects (Chi et al., 2019). Consequently, TCM has become a prominent area of scientific investigation for the management of depressive disorders.

Autophagy is a crucial intracellular degradation mechanism where cellular components are transported and broken down in lysosomes. Additionally, autophagy functions as a dynamic circulatory system that generates fresh molecular constituents and energy to maintain cellular renewal and homeostasis (Mizushima and Komatsu, 2011). Dysregulation of autophagy is significant for understanding of both the physiological and pathological aspects of several nervous system disorders, including depression. Accumulating evidence from clinical and preclinical studies demonstrated the significant role of autophagy modulation in depression (Jia and Le, 2015; Gassen and Rein, 2019). Therefore, it is important to design a novel treatment strategy for patients with depression by regulating autophagy.

The review focuses on the initiation steps of autophagy, its connection to depression, and its pathological mechanisms. It also summarizes the pharmacological mechanisms of antidepressants by regulating autophagy, providing a scientific basis for their future use in clinical applications.

2 The relationship between autophagy and depression

2.1 Classification of autophagy

Autophagy is a cellular breakdown process that targets aged organelles or macromolecules, including viruses and bacteria, within eukaryotic cells. It plays a crucial role in alleviating cellular developmental disorders (Levine et al., 2011; Zhou et al., 2020). Autophagy includes three main forms: macro-autophagy, micro-autophagy, and chaperone-mediated autophagy. These forms facilitate the breakdown and recycling of cytosolic components, functioning similarly to lysosomes. Micro-autophagy can be further classified into selective, nonselective, and endosomal forms types, which involve lysosomal depression, lysosomal protrusion, and endosomal depression based on membrane dynamics. The primary mechanism involves the formation of arm- or petal-like protrusions by the lysosomal membrane, which enclose cytoplasmic portions or organelles for degradation (Oku and Sakai, 2018). Chaperone-mediated autophagy, mediated by the chaperone heat shock 70 (HSC70) protein and other proteins, selectively degrades proteins carrying KFERQ-like motifs and transfers them to lysosomes via lysosomal receptors (Dice, 1990). Chaperone-mediated autophagy (CMA) is a crucial process involved in the progression of tumor development, malignant transformation, and neurodegeneration (Gomes et al., 2017).

Macro-autophagy, commonly referred to as autophagy, is the way for cytosolic components to reach lysosomes. It is a distinct multi-step mechanism of membrane transport where cytosolic components and organelles are engulfed and destroyed by double-membrane structures. Autophagy is strictly regulated to maintain an equilibrium between the synthesis and destruction of cellular components, as well as their use and recycling. Abnormal expression of regulatory genes and lysosomal dysfunction can lead to abnormal autophagy. Macro-autophagy is involved in cardiovascular diseases, aging, neurodegenerative diseases, cancer, infectious and inflammatory diseases, and proceeds through initiation, nucleation, extension, fusion, and degradation (Ravanan et al., 2017).

2.1.1 Initiation

Under stress conditions, cells form crescent-shaped bilayer membranes called phagophores in the cytosol, indicating the beginning of autophagy. Bilayer membranes may originate from various sources such as the mitochondrial membrane, endoplasmic reticulum membrane, Golgi membrane, cytoplasmic membrane, ER-mitochondrial contact sites, ER-Golgi intermediates, or recycling endosomes (Ge et al., 2015; Søreng et al., 2018). Autophagy initiation is mediated by unc51-like autophagy-activating kinase 1 (ULK1). Under physiological conditions, mTOR complex 1 (mTORC1) hyperphosphorylates autophagy-related gene (ATG)13 and mammalian ATG1 homologs (ULK1 and ULK2), inhibiting kinase activity of ULK, and preventing the interaction of ATG13 with ULK and FIP200 (a scaffold protein), thus inhibiting autophagy in mammalian cells (Wang et al., 2018a). Stress exposure leads to the dissociation of mTORC1 from the ULK1/ATG1 complex (comprised by ULK1, FIP200, ATG13, and ATG101), allowing ULK1 to anchor to the autophagy precursor structure (PAS), thereby initiating the process of autophagy (Yamamoto et al., 2016).

2.1.2 Nucleation

After the initiation of autophagy, nucleation occurs under the action of vacuum protein sorting 34 (VPS34) and the Beclin-1 complex. VPS34, a type III phosphatidylinositol (PI) kinase, converts PI into PI trisphosphate (PI3P) through phosphorylation. Beclin-1, a pivotal protein within the type III Phosphoinositide 3-kinase (PI3K) complex, regulates autophagosome maturation by binding to VPS3 and its co-factors. Acetylation of VPS34 determines the success or failure of autophagy nucleation. Acetylation at the K29 site hinders the assembly of the core complex including VPS34 and Beclin-1, while acetylation of the K771 site weakens the binding between VPS34 and its substrate, PI. Acetylation of K781 reduces the activity of VPS34 kinase (Su et al., 2017).

2.1.3 Elongation

The expansion of autophagic vacuoles relies on two ubiquitin-like binding systems: the ATG5-ATG12-ATG16L1 conjugation pathway and the ATG8 lipidation pathway. The ATG5-ATG12-ATG16L1 complex plays a crucial role in elongating autophagic vacuoles and acts as a platform for ATG8 lipidation (Ohsumi, 2001; Fujita et al., 2008; Fahmy and Labonté, 2017). This aids in the formation of vesicles surrounded by bilayer membranes. Additionally, the ATG4 enzyme cleaves ATG8 proteins (light chain 3 [LC3], GABA type A receptor–associated protein [GABARAP]l1, and GABARAP, et al.), resulting in the formation of LC3I, which represents the cytosolic variant of LC3. ATG7 then conjugates LC3I to phosphatidylethanolamine, forming LC3II, which remains associated with the autophagosome membrane. The LC3II/LC3I ratio serves as an indicator of autophagic activity (Suzuki et al., 2013).

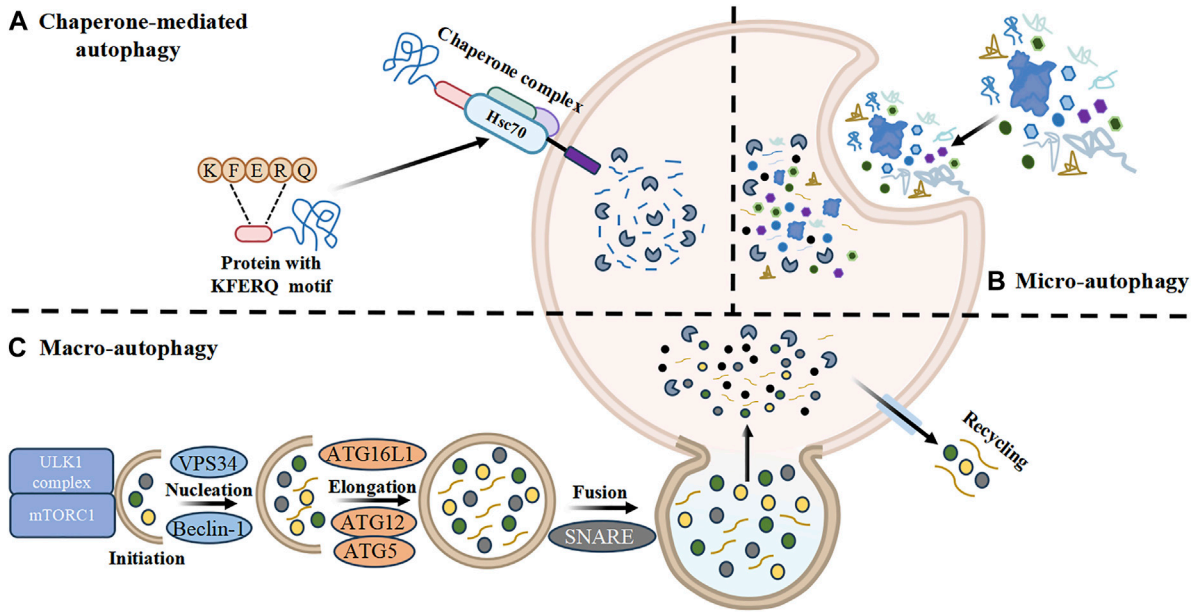


FIGURE 1
Classification and corresponding processes of autophagy. **(A)** Chaperone-mediated autophagy. Chaperone-mediated autophagy is mediated by the chaperone heat shock 70 (HSC70) protein and other proteins that selectively degrade proteins carrying KFERQ-like motifs and transfer them to lysosomes for autophagy via lysosomal receptors. **(B)** Micro-autophagy. The primary method entails the formation of arm- or petal-like protrusions by the lysosomal membrane, which envelops a portion of the cytoplasm or organelles in order to encase the molecules targeted for degradation. **(C)** Macro-autophagy. Macro-autophagy is the primary method via which cytosolic components reach lysosomes. Macro-autophagy steps include initiation, nucleation, extension, fusion, and degradation. HSC70, Heat shock 70 protein; ULK1, Unc51 like autophagy activating kinase; mTORC1, mTOR complex 1; ATG, Autophagy related genes; SNARE, Soluble NSF attachment protein receptor.

2.1.4 Fusion and degradation

The fusion of autophagosomes with endosomes or lysosomes is a crucial process for the elimination of cellular debris. Studies have demonstrated that the soluble N- ethylmaleimide-sensitive factor (NSF) attachment protein receptor (SNARE) protein family can mediate the fusion of autophagosomal and lysosomal membranes, promoting the maturation of autophagosomes (Shen et al., 2021). Finally, the outer membrane of the autophagosome fuses with the lysosomal membrane to form an autolysosome, allowing lysosomal hydrolases to degrade autophagic cargoes and release the recovered nutrients (such as amino acids and lipids) back into the cytoplasm for reuse (Galluzzi and Green, 2019) (Figure 1).

2.2 Autophagy's role in the development of depression

A growing body of research has established a correlation between autophagy and depression. Dysregulation of autophagy-related gene expression was observed in blood monocytes of patients diagnosed with MDD during a clinical trial (Alcocer-Gómez et al., 2017). Furthermore, abnormal expression of AKT1 and mTOR signaling pathways, which regulate autophagy, has been found in patients with depression (Jernigan et al., 2011; Machado-Vieira et al., 2015). In *postpartum* depression (PPD) patients, changes in extracellular vesicle mRNA, potentially related to autophagy, suggest that interruption of extracellular vesicle mRNA communication may be involved in the pathological development of PPD (Osborne et al., 2022). Bioinformatics techniques have identified potential diagnostic markers for MDD, including autophagy-related genes such as GPR18, PDK4, NRG1, and EPHB2. Additionally, GPR18 may play a role in the pathological progression of MDD (He et al., 2021).

Preclinical investigations have demonstrated the involvement of autophagy in various pathways related to the pathophysiology and progression of depression. There is substantial evidence supporting the association between depression and inflammatory mechanisms (Kohler et al., 2016). Inflammation increases vulnerability to depression, as individuals diagnosed with depression exhibit elevated levels of pro-inflammatory markers, and the utilization of pro-inflammatory medications amplifies the likelihood of depression occurrence (Kohler et al., 2016). Conversely, the administration of antidepressant medication has been observed to decrease peripheral concentrations of inflammatory cytokines (Liu et al., 2020a). The NOD-like receptor pyrin domain-containing 3 (NLRP3) inflammasome is a protein complex that triggers the caspase-1-mediated proteolytic activation of pro-inflammatory cytokines belonging to the interleukin-1β (IL-1β) family, as well as the apoptosis in inflammatory cells, significantly contributing to depression progression (Mangan et al., 2018; Yu et al., 2023). Notably, autophagy is closely linked to the activation of the NLRP3 inflammasome. Dysfunctional lysosomes in the autophagy-lysosome pathway disrupt the degradation of the NLRP3 inflammasome, leading to the generation of pro-inflammatory factors. This process can induce depression-like behavior in mice (Li et al., 2022a). High-mobility group box 1

(HMGB1) has been identified as an early warning protein that induces inflammatory responses after stress exposure (Young et al., 2023). Microglia are a type of cellular component that originates from the mesodermal layer of neural tissue. The primary origin of pro-inflammatory cytokines and inflammation-related proteins under the control of several intracellular signals can be attributed to activated microglia (Park et al., 2023). Activation of the HMGB1/signal transducer and activator of transcription 3 (STAT3)/nuclear factor-kappa B (NF-κB) p65 axis in microglia located in the medial prefrontal cortex (mPFC) facilitates microglial activation and autophagy, contributing to the pathophysiology and progression of depression (Xu et al., 2023). Mechanistic studies have revealed that under physiological conditions, autophagy inhibits excessive activation of the NLRP3 inflammasome and its secreted pro-inflammatory cytokines. Additionally, autophagy plays an important role in the anti-inflammatory process by activating immune cells to produce pro-inflammatory mediators (Zhu and Liu, 2022).

Neurogenesis refers to the process through which neural stem cells (NSCs) or neural progenitor cells (NPCs) generate new neurons. This phenomenon occurs not only during the embryonic and perinatal stages but also in two distinct regions of the mammalian central nervous system: the subventricular zone (SVZ) located in the lateral ventricle and the subgranular zone (SGZ) situated in the dentate gyrus of the hippocampus (Yao et al., 2016). Impaired neurogenesis is believed to underlie the pathogenesis of psychiatric disorders, particularly depression (Kempermann, 2002). In patients with depression, decreased granule cell numbers and volume in the anterior and middle dentate gyrus (DG) were observed, while neurogenesis increased and depressive symptoms improved after antidepressant treatment (Mahar et al., 2014). Autophagy and neurogenesis have also been reported in depression models. Chronic constraint stress is commonly used to induce depression in animal models. Autophagic cell death in NSCs and impaired adult hippocampal neurogenesis have been observed in mice subjected to an induced depression model (Jung et al., 2020). In a corticosterone (CORT)-induced depression model, excessive neuronal autophagy activity was observed in the DG region of the brain, upregulating the expression of ATG5. This led to significant degradation of brain-derived neurotrophic factor (BDNF), which had a detrimental effect on the proliferation of NSCs, NPCs, and neuroblasts. Furthermore, the survival and migration of newly generated immature and mature neurons in the DG were impaired. However, suppression of ATG5 in neurons alleviated these pathological phenomena, leading to an improvement in depression-like behavior in mice (Zhang et al., 2023a). BDNF is a growth factor that plays a crucial role in neuronal development, synapse formation, and synaptic plasticity in the brain (Björkholm and Monteggia, 2016). According to the neurotrophic theory, reduced BDNF expression deprives neurons of necessary nutrition, resulting in neuronal atrophy, decline in synaptic plasticity, and the onset of depression (van Zutphen et al., 2019). Nevertheless, the normalization of BDNF levels plays a significant role in promoting synaptic plasticity, enhancing neuronal repair, and mitigating depression symptoms (Phillips, 2017). Mechanistic studies have shown that a glucocorticoid-induced stress response enhances the expression of the stress-responsive co-chaperone FK506-binding protein 51, activates autophagy, and promotes extracellular BDNF maturation through increased matrix metalloproteinase 9 (MMP9) secretion (Martinelli et al., 2021).

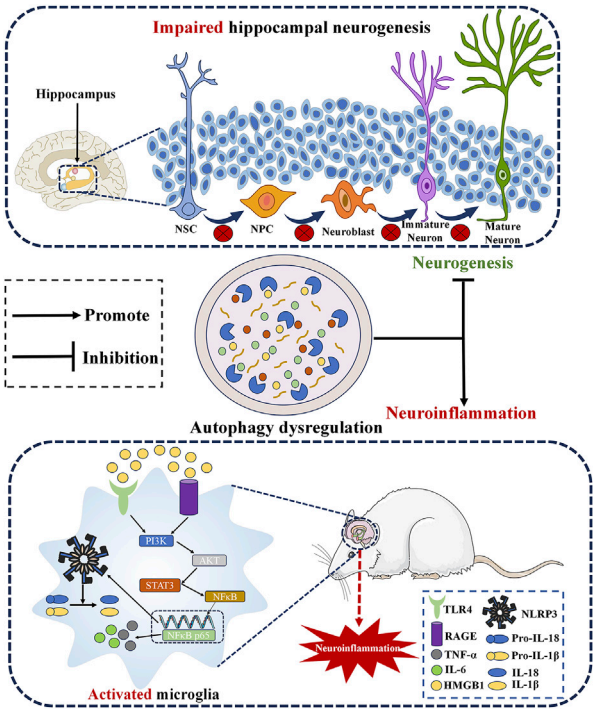


FIGURE 2
Microscopic pathological mechanism of autophagy induced depression. Autophagy dysregulation participates in the pathological development of MDD by addressing hippocampal neurogenesis and neuroinflammation. NSC, Neural stem cell; NPC, Neural progenitor cell; NLRP3, NOD-like receptor pyrin domain containing 3; IL-1β, Interleukin-1β; HMGB1, High molecular group box 1; NF-κB, Nuclear factor-kappa B; IL-6, Interleukin-6; TNF-α, Tumor necrosis factor-α; TLR4, Toll-like receptors 4; RAGE, advanced glycation end products.

Obesity is characterized by excessive accumulation and storage of body fat, leading to weight gain (Atawia et al., 2019). Numerous reports highlight the association between depression and obesity as a major public health concern (Silva et al., 2020). MDD is particularly common in individuals with severe obesity (i.e., class II-III) (Faulconbridge et al., 2018). In an experimental model of obesity induced by a high-fat diet, it was observed that obesity impairs autophagy by inhibiting the phosphorylation of adenylate-activated protein kinase (AMPK) and promoting the phosphorylation of mTOR. This disruption in cellular signaling pathways contributes to the development of depression-like behavior (Li et al., 2022b) (Figure 2).

3 Mechanism of antidepressant chemicals regulating autophagy

3.1 Chemicals acting on nervous system diseases

Neurotransmitters in the central nervous system, such as catecholamines (dopamine [DA], norepinephrine [NE], and epinephrine [E]) and indoleamines (serotonin [5-HT]), play a crucial role in emotional regulation, cognition, and sleep

(Berke, 2018). Dysregulation of these neurotransmitters can lead to various emotional alterations (Wang et al., 2021a). According to the traditional monoamine hypothesis, depression is caused by a reduction in monoamine neurotransmitters inside the central nervous system. Assessing the levels of these neurotransmitters and their metabolites in the serum can serve as significant diagnostic biomarkers for depression. Pharmacological interventions that increase synaptic concentrations of monoamines have shown efficacy in alleviating depressive symptoms (Wang et al., 2019a). Fluoxetine, a selective SSRI is widely used in clinical practice. Studies have demonstrated that fluoxetine can reverse depressive-like symptoms by activating the nuclear factor erythroid-derived 2-like 2 (Nrf2)-dependent gene expression, reducing neuronal autophagy and cell death in the hippocampus, and mitigating lipopolysaccharide (LPS)-induced peripheral inflammation in mice (Ghosh et al., 2020). Another study found that fluoxetine promotes astrocytic autophagy in a p53-dependent manner and improves mitochondrial damage both *in vivo* and *in vitro* (Shu et al., 2019). Furthermore, fluoxetine therapy has been reported to improve depression-like behavior induced by olfactory bulb resection in rats, reversing hippocampal metabolic disorder and autophagy inhibition (Zhou et al., 2019). PPD is a prevalent psychological condition that occurs after childbirth and poses detrimental effects on maternal wellbeing, with approximately 20% of *postpartum* deaths attributed to suicide resulting from PPD (Payne and Maguire, 2019). Inhibition of autophagy in microglia contributes to the production of inflammation, exacerbating PPD. Fluoxetine has been shown to mediate the autophagy pathway and upregulate the expression of BDNF, offering potential treatment for PPD (Tan et al., 2018).

Agomelatine, a pharmacological compound structurally similar to melatonin, exerts its antidepressant effects by activating melatoninergic receptors (MT1 and MT2) and inhibiting 5-HT2C receptors. These mechanisms contribute to its antidepressant effects (Maddukuri et al., 2021). Research has indicated that agomelatine can regulate neuroinflammation, apoptosis, and autophagy induced by LPS through the inhibition of the G alpha i (2) (Gαi-2)/protein kinase A (PKA)/apoptosis signal-regulating kinase 1 (ASK1) pathway, thereby exhibiting antidepressant properties (Lan et al., 2022). Ketamine, a pharmacological agent acting as a noncompetitive antagonist of the N-methyl-D-aspartate receptor (NMDAR), preferentially inhibits NMDARs containing the GluN2B subunit, mainly found in inhibitory GABAergic interneurons (Sato et al., 2022). Studies have shown that ketamine, even at sub-anesthetic doses (10 mg/kg), exerts an antidepressant effect by inhibiting inflammation and activating autophagy initiation (Lyu et al., 2022). As an emerging mechanism of cellular demise, ferroptosis, is primarily distinguished by cytological alterations. When the ferroptosis pathway is activated, it can trigger depressive symptoms (Mou et al., 2019; Xu et al., 2022). Ketamine has been shown to induce autophagy, improve neuroplasticity, inhibit ferroptosis (Zhang et al., 2022), regulate the autophagic flux of microglia through the HMGB1-advanced glycation end products (RAGE) receptor pathway, and modulate microglial polarization (Wu et al., 2022).

3.2 Chemicals regulating endocrine metabolism

Carbagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor used as an antidiabetic drug, has gained attention due to its additional cardiovascular benefits (Du et al., 2022). In a recent preclinical investigation, the efficacy of canagliflozin in ameliorating depression-like behavior induced by chronic unexpected mild stress (CUMS) in rats was examined. The results revealed that canagliflozin modulates the AMPK/mTOR autophagy signaling pathway, exhibits anti-inflammatory and neuroprotective effects, and alleviates depressive symptoms (Khedr et al., 2023).

Rosiglitazone, a thiazolidinedione (TZD) used as an antidiabetic drug because of its insulin sensitivity, acts by activating the intracellular receptor class of peroxisome proliferator-activated receptor gamma (PPARγ) (Fryklund et al., 2022). Previous studies have shown the effectiveness of rosiglitazone in alleviating depression-like symptoms in animal models (Sharma et al., 2012; Zong et al., 2018). Additionally, rosiglitazone improves dexamethasone-induced depression in mice through the regulation of cerebral glucose metabolism and the AMPK/mTOR signaling pathway (Alhaddad et al., 2023). The mTOR signaling pathway plays a crucial role in the control of autophagy. A comprehensive investigation utilizing both *in vivo* and *in vitro* approaches elucidated the underlying mechanism by which rosiglitazone exerts therapeutic effects on depression. It was found that rosiglitazone promotes neuroprotection by upregulating autophagy and inducing excessive apoptosis in astrocytes affected by depression (Zhao et al., 2017).

Metformin, the first-line therapy for type 2 diabetes, mediates blood glucose control through hepatic gluconeogenesis and has pleiotropic effects on glucose metabolism (LaMoia and Shulman, 2021). Metformin also plays a significant role in the therapeutic management of depression. Studies have reported that metformin can modulate microbiota-derived inosine levels, ameliorate anxiety and depression-like withdrawal symptoms caused by methamphetamine in mice (Yang et al., 2022a), and potentially reduce the likelihood of depressive symptoms compared to other oral hypoglycemic medications (Yu et al., 2022a). In a recent study, metformin was found to improve depression-like behavior in a mouse model of Parkinson's disease by increasing protein expression in the autophagy signaling pathway and promoting autophagosome formation (Mendonça et al., 2022).

Atorvastatin, a statin lipid regulator, inhibits cholesterol production, resulting in reduced blood cholesterol levels and decreased cardiovascular risk (Yu et al., 2022b). Previous studies have demonstrated that atorvastatin can prevent LPS-induced depression-like behavior (Taniguti et al., 2019) and activate autophagy while relieving oxidative stress through acting on NADPH oxidase 2 (NOX2), thereby improving depression-like behavior in mice with Parkinson's disease (Yan et al., 2020).

3.3 Other types of chemicals

Hydrogen sulfide (H_2S) is an endogenous gaseous transmitter that can be produced internally in mammals through four enzymatic pathways (Wu et al., 2018). Intervention of H_2S is used to treat depression as it counteracts the depressive and anxiety-related

effects caused by sleep deprivation (Kang et al.). It achieves this by inhibiting neuroinflammation via a silent mating-type information regulation 2 homolog 1 (SIRT1)-dependent mechanism (Kang et al.). Furthermore, studies have indicated that inhibiting inflammation and ferroptosis may potentially alleviate depression-like behavior in rats with type 1 diabetes (Wang et al., 2021b). H_2S has been reported to alleviate depressive behavior by increasing adiponectin levels, thereby improving hippocampal synapse formation dysfunction and excessive autophagy (Tian et al., 2018). Moreover, the antidepressant properties of H_2S are attributed to its ability to enhance the activity of the brain-derived neurotrophic factor-tropomyosin-related kinase B (TrkB) pathway in the hippocampus, thus facilitating autophagy (Liu et al., 2020b).

Roflumilast, a highly effective and specific inhibitor of phosphodiesterase-4 (PDE4), has shown potential in reducing exacerbations in individuals suffering from severe chronic obstructive pulmonary disease (COPD) accompanied by chronic bronchitis or a history of exacerbation (Wedzicha et al., 2016). Roflumilast activates the AMPK/mTOR/ULK1 autophagy pathway and provides neuroprotective effects in the treatment of depression (Zaki et al., 2023). Resolvin D1 (RvD1) is a lipid mediator with notable anti-inflammatory properties derived from docosahexaenoic acid (DHA), an omega-3 polyunsaturated fatty acid, synthesized endogenously in the organism (Roohbakhsh et al., 2022). Studies in mice have demonstrated that RvD1 induces microglial autophagy, suppresses M1 polarization and inflammatory response, reduces neurotoxicity, and ameliorates depression-like behavior (Xiong et al., 2023).

Bafilomycin A1, an organic macrolide antibiotic derived from *Streptomyces* griseus, specifically inhibits vacuolar H^+-ATPase, impeding the acidification process in organelles housing this enzyme (Xu et al., 2020). The antidepressant properties of Bafilomycin A1 are attributed to its ability to counteract apoptosis, autophagy, and neuroinflammation in the hippocampus (Wang et al., 2018b). Melatonin, a hormone of the indole class synthesized in the pineal gland via the tryptophan-serotonin biosynthetic pathway, is regulated by the brain's circadian clock (Vasey et al., 2021). Melatonin exhibits antidepressant effects in an LPS-induced animal depression model, and its mechanism involves regulating autophagy through the Forkhead box o (FOXO) 3a signaling pathway (Ali et al., 2020).

Vitamin E (VE), an essential vitamin discovered in the 1920s, is widely used for its antioxidative properties. VE encompasses a group of eight lipid-soluble molecules, including alpha, beta, gamma, and delta forms of tocopherols, with alpha-tocopherol being the predominant variant (Miyazawa et al., 2019; Yang et al., 2020). Alpha -Tocopherol has been proven to promote autophagy in mice subjected to CUMS through the AMPK/mTOR pathway, thereby mediating antidepressant effects (Huang et al., 2018a) (Table 1).

4 Treatment of depression by regulating autophagy using TCM

4.1 Active compounds of TCM

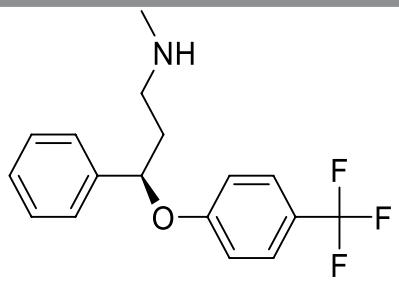
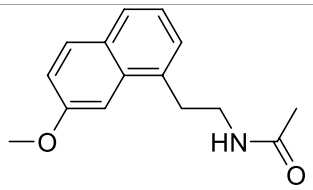
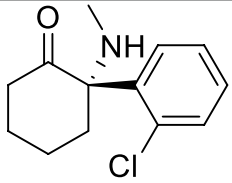
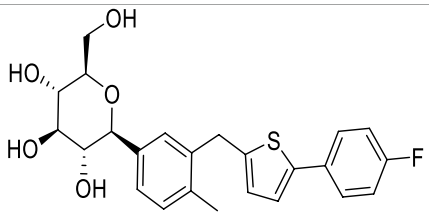
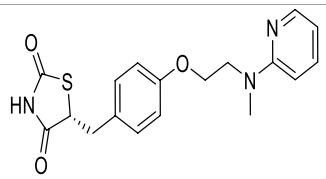
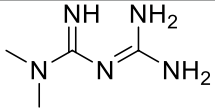
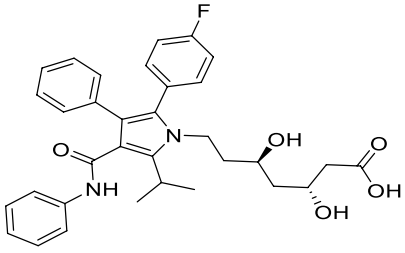
Resveratrol, a phenolic compound originally derived from Veratrum grandiflorum, is abundantly present in grapes, wine, peanuts, soybeans, and berries. Its therapeutic potential in the context of depression has attracted significant attention from researchers and medical professionals (Breuss et al., 2019). Extensive research has been conducted on the use of resveratrol for treating depression (Moore et al., 2018). Studies have found that CUMS can inhibit the activity of the SIRT1 signaling pathway in mice, resulting in downregulation of autophagy and mitophagy-related protein expression, and neuronal damage. However, treatment with resveratrol can alleviate these pathological phenomena (Tabassum et al., 2023). In a mouse model of PPD, intragastric administration of resveratrol alleviated depressive behavior by stimulating SIRT1, inducing autophagy, and inhibiting the AKT/mTOR signaling pathway (Ye et al., 2023).

Oridonin is the principal bioactive constituent within the Chinese botanical remedy *Rabdosia rubescens*, demonstrating significant anti-inflammatory properties. It exhibits considerable anticancer activities by inducing cell cycle arrest andapoptosis, and inhibiting angiogenesis (He et al., 2018). Previous studies have shown that oridonin can regulate the signal of PPAR-γ and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid glutamate receptors (AMPARs) in the prefrontal cortex to treat depression (Liu and Du, 2020). Recent studies have found that the antidepressant effect of oridonin involves blocking the interaction between NLRP3 and NIMA-related kinase 7 (NEK7) to inhibit neuroinflammation and autophagy injury (Liang et al., 2022). Additionally, oridonin can inhibit the NLRP3 inflammasome by activating autophagy to alleviate depressive symptoms caused by LPS (Li et al., 2022c). Previous studies have also demonstrated that *Scutellaria baicalensis* exerts an antidepressant effect by reducing the expression of LC3-B (a marker of the autophagy pathway) in neurons of the hippocampal CA1 region (Li et al., 2021). Baicalin, a flavonoid derived from the desiccated roots of *S. baicalensis*, exhibits diverse pharmacological properties (Shen et al., 2019). It intervenes in depression through multiple targets and channels (Liu et al., 2019). Importantly, baicalin enhances Nip-like protein (NIX)-mediated mitophagy by activating the AMPK/peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α pathway to treat depression (Jin et al., 2023).

Morinda officinalis, a type of TCM grown in Southeast China, effectively strengthens bones, tonifies the kidneys, and treats impotence, menstrual disorders, and inflammatory diseases. *Morinda officinalis oligosaccharide* is one of its main effective components that can alleviate depression-like behavior by regulating intestinal microbes (Chi et al., 2020). Interestingly, in an animal model of hypertension with depression, *M. officinalis oligosaccharide* increased the expression of mitofusion 2 (Mfn2) to activate mitophagy mediated by the PI3K/AKT/mTOR pathway, thereby playing a protective role on astrocytes (Yang et al., 2023). *Andrographis paniculata* is a traditional herbal medicine commonly used in Asian countries to relieve symptoms caused by colds (Burgos et al., 2020). Andrographolide is one of its active ingredients and has anti-inflammatory, antitumor, antiviral, and antifibrotic effects (Zhang et al., 2021a). More importantly, andrographolide activates autophagy to inhibit inflammation and improve depression-like behavior induced by CUMS in mice (Geng et al., 2019).

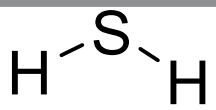
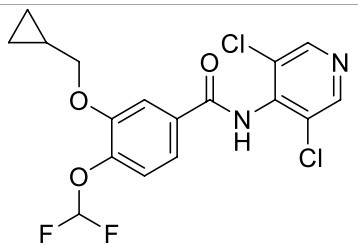
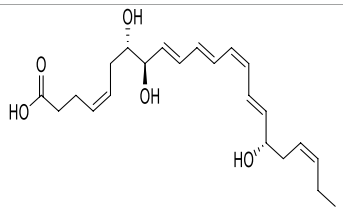
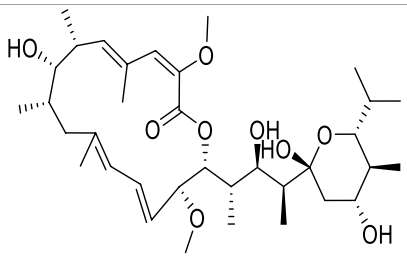
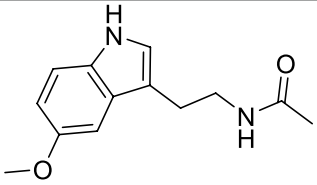
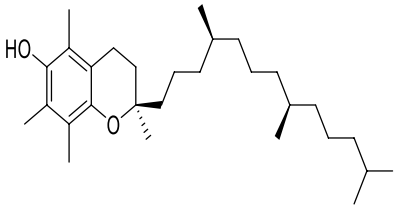
Allicin, a naturally occurring compound found in the bulbs of plants belonging to the Liliaceae family, has been studied for its

TABLE 1 Regulation of antidepressant chemicals on autophagy.

Antidepressant chemical	Chemical structure	Regulating autophagy mechanism	References
Fluoxetine		Activating the hippocampal Nrf2 pathway to reduce autophagy activity and alleviate cell death	Shu et al. (2019)
		Promote autophagy, alleviate mitochondrial damage, and alleviate the pathological damage of hippocampal astrocytes	Shu et al. (2019)
		Activating hippocampal autophagy and improving hippocampal metabolic disorders	Zhou et al. (2019)
		Mediates antidepressant via autophagy pathway and upregulates BDNF levels	Tan et al. (2018)
Agomelatine		Inhibition of Gαi-2/PKA/ASK1 pathway activity to anti inflammation and regulate autophagy activity	Lan et al. (2022)
Ketamine		Inhibit inflammation and activate autophagy	Lyu et al. (2022)
		Triggering autophagy, improving neuroplasticity, and inhibiting ferroptosis	Zhang et al. (2022)
		Regulates the autophagic flux of microglia and microglial polarization through the HMGB1/RAGE pathway	Wu et al. (2022)
Carbagliflozin		Regulating AMPK/mTOR autophagy signaling pathway and its anti-inflammatory and neuroprotective effects	Khedr et al. (2023)
Rosiglitazone		Regulation of brain glucose metabolism and AMPK/mTOR signaling pathway	Alhaddad et al. (2023)
		Upregulate autophagy level to exert neuroprotective effect and alleviate excessive apoptosis of astrocytes	Zhao et al. (2017)
Metformin		Increase protein expression of autophagy signaling pathways and promote autophagosome formation	Mendonça et al. (2022)
Atorvastatin		Acting on NOX2 to activate autophagy and alleviate oxidative stress	Yan et al. (2020)

(Continued on following page)

TABLE 1 (*Continued*) Regulation of antidepressant chemicals on autophagy.

Antidepressant chemical	Chemical structure	Regulating autophagy mechanism	References
H_2S		Upregulation of adiponectin levels, improvement of hippocampal synaptic dysfunction, and relief of excessive autophagy	Tian et al. (2018)
		Enhancing the activity of hippocampal BDNF/TrkB signaling pathway to promote autophagy	Liu et al. (2020b)
Roflumilast		Activating the AMPK/mTOR/ULK1 autophagy pathway and exerting neuroprotective effects	Zaki et al. (2023)
Resolvin D1		Promote autophagy of microglia, inhibit M1 polarization and inflammatory response, and reduce neurotoxicity	Xiong et al. (2023)
Bafilomycin A1		Regulating cell apoptosis, autophagy, and neuroinflammation in the hippocampus	Wang et al. (2018b)
Melatonin		Autophagy activity regulating the FOXO3a signaling pathway	Ali et al. (2020)
α- tocopherol		Promoting autophagy by acting on the AMPK/mTOR pathway	Huang et al. (2018a)

Nrf2, nuclear factor (erythroid-derived 2)-like 2; BDNF, brain-derived neurotrophic factor; Gαi-2/PKA/ASK1, G alphai (2)/protein kinase A/apoptosis signal-regulating kinase 1; HMGB1/RAGE, High molecular group box 1/advanced glycation end products; AMPK/mTOR, adenylate-activated protein kinase/mammalian target of rapamycin; TrkB, brain-derived neurotrophic factor-tropomyosin-related kinase B; ULK1:unc51 like autophagy activating kinase 1; FOXO3a, Forkhead box O 3a.

potential therapeutic properties, including anticancer, antihypertensive, hypoglycemic, and lipid-lowering effects (Shi et al., 2019). It can also alleviate depression-like symptoms caused by a high-fat diet. Its mechanism involves improving mitochondrial function to regulate autophagy, relieve oxidative stress, and optimize NOX/Nrf2 imbalance, thereby reducing insulin resistance in the hippocampus (Gao et al., 2019). Salvianolic acid B, a phenolic acid derived from the desiccated roots and rhizomes of *Salvia miltiorrhiza*, has extensive usage in managing cardiovascular and cerebrovascular ailments (Li et al.,

2020). It also plays an important role in the nervous system, particularly in depression. Studies have demonstrated that salvianolic acid B enhances autophagy and facilitates the elimination of the NLRP3 inflammasome, thereby eliciting neuroprotective and antidepressant effects (Jiang et al., 2017).

Patchouli alcohol, a tricyclic sesquiterpene, is a natural compound found in *Pogostemon cablin* that possesses various beneficial pharmacological effects (Lee et al., 2020). The activation of the mTOR signaling pathway plays a crucial role in regulating autophagy and exerting antidepressant effects (Zhuo et al., 2020). *Lotus plumule*, which refers to the green embryo found in lotus seeds, is a traditional medicinal substance commonly consumed in China as tea. It is believed to possess properties that can alleviate symptoms of irritability and hypertension (Xiong et al., 2016). Network pharmacology, distinguished by its emphasis on integrity and systematicity, utilizes high-throughput screening, network visualization, and analysis to explore intricate connections between drugs, targets, and diseases. This approach proves advantageous in advancing the research and development of TCM (Wang et al., 2021c). Using network pharmacology and experimental verification, Chen et al. discovered that bioactive alkaloids from *Lotus plumule* inhibit neuroinflammation and alleviate LPS-induced depressive behavior by mediating BDNF-driven endoplasmic reticulum (ER) stress and autophagy (Chen et al., 2019). Quercetin, a flavonoid compound possessing antioxidant, antiviral, antibacterial, and anti-inflammatory properties, is abundantly found in various fruits and vegetables (Di Petrillo et al., 2022). Studies have shown that the antidepressant effect of quercetin is the result of protecting neurons by promoting mitophagy to inhibit the activation of the NLRP3 inflammasome mediated by mitochondrial reactive oxygen species (mtROS) in microglia (Han et al., 2021).

Euryale ferox, a plant with a long history of use in TCM, has primarily been employed to enhance renal function, invigorate vital essence, and strengthen the spleen to alleviate symptoms of diarrhea. This treatment modality is frequently observed in managing various medical conditions, including spermatorrhea, gonorrhea, dysmenorrhea, urinary incontinence, and fecal incontinence (Jiang et al., 2023). The petroleum ether fraction of *E. ferox* activates autophagy through the regulation of the AMPK pathway, exhibiting therapeutic effects in animal models of depression (Huang et al., 2018b). Apigenin, a flavonoid widely present in fruits and vegetables, is associated with numerous health advantages (Majma Sanaye et al., 2022). Similarly, apigenin has been shown to promote autophagy and improve depression through the AMPK/mTOR signaling pathway (Zhang et al., 2019).

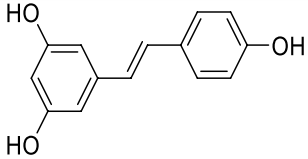
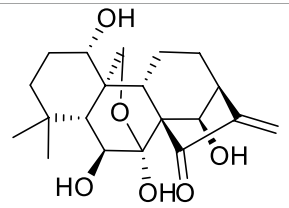
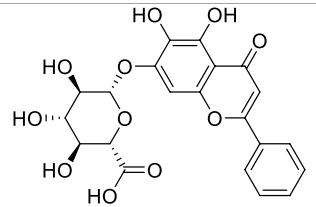
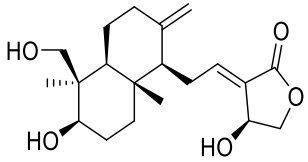
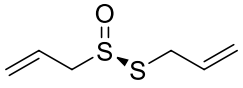
Ginsenoside Rg1, a protopanaxatriol saponin, is abundantly found in ginseng products and extensively investigated in the context of endocrine disorders (Liu et al., 2017). The antidepressant mechanism of Ginsenoside Rg1 involves the effects on ubiquitin-proteasome and autophagy-lysosome degradation pathways of connexin 43 (Cx43) (Wa et al., 2021). Aconite and its active components are commonly used for treating depression (Liu et al., 2012). The coalescence of aggregate alkaloids found in aconite and ginsenosides regulates autophagy and hippocampal synaptic plasticity through the activation of the BDNF-mTORC1 signaling pathway, contributing to the manifestation of an antidepressant effect (Jin et al., 2022). Silibinin, an active compound extracted from Compositae *plant milk thistle*, has various pharmacological effects, including anti-inflammatory, antioxidant, and antifibrotic activities (Jiang et al., 2021). Studies have provided evidence indicating that silibinin mitigates neuronal damage by modulating the BDNF/TrkB pathway while reducing the extent of autophagy in the hippocampus (Song et al., 2017). *Radix Polygalae*, a renowned Chinese herbal medicine, has been utilized in China for numerous purposes over several centuries, including as an expectorant, tonic, sedative, and antipsychotic agent (Jiang et al., 2021). The extract inhibits neuroinflammation and treats depression by promoting autophagy (Zhou et al., 2021) (Table 2).

4.2 TCM compounds

Xiaoyaosan (XYS) is a TCM formulation documented in the monograph titled "Prescription of the Taiping People's Welfare Pharmacy Bureau" during the Northern Song Dynasty (960–1127 AD). It consists of Chaihu (*Radix Bupleuri*), Danggui (*Radix Angelicae Sinensis*), Baishao (*Radix Paeoniae Alba*), Baizhu (*Rhizoma Atractylodis Macrocephalae*), Fuling (*Poria*), Bohe (*Herba Menthae Haplocalyx*), Shengjiang (*Rhizoma Zingiberis*), and Gancao (*Radix Glycyrrhizae*). Currently, various strategies are available for the treatment of depression. TCM compounds, including XYS, have demonstrated antidepressant effects in both clinical and preclinical studies (Wang et al., 2023). In a recent report, XYS was found to regulate autophagy and the expression of glucose transporter-4 (GLUT4) in hypothalamic neurons of depressed mice (Yang et al., 2022b). Moreover, modified XYS alleviated neuronal apoptosis by triggering autophagy and effectively treated depression-like behavior caused by CUMS (Wang et al., 2019b). Another study discovered that modified XYS inhibits M1 polarization of microglia and alleviates neuroinflammation by activating the PI3K/AKT/mTOR pathway to induce autophagy (Su et al., 2023). The MingmuXiaoyao granule, a modified compound derived from XYS, has been observed to regulate autophagy through modulation of the PI3K/AKT/mTOR signaling pathway, thereby enhancing retinal morphology and function, as well as alleviating depression-like behavior in rats subjected to CUMS (Ma et al., 2022).

Lily Bulb and Rehmannia Decoction is a specialized medicinal formulation utilized for the therapeutic management of "lily disease," characterized by symptomatology similar to clinical depression (Zhang et al., 2020). Metabolomics analyzes metabolites in biological cells or tissues, identifies abnormal metabolic networks associated with diseases, analyzes data collected by instruments through multivariate statistical methods to identify differential metabolites and describe changes in metabolic pathways. This approach helps explain the response mechanism of organisms to corresponding stimuli (Johnson et al., 2016). The integration of network pharmacology and metabolomics offers a promising approach for comprehensively unraveling the therapeutic mechanisms underlying TCM in the context of affective disorders such as depression (Liu et al., 2021; Qu et al., 2021). Chi et al. demonstrated that treatment with Lily Bulb and Rehmannia Decoction alleviated LPS-induced depression-like behavior in rats. They also found that autophagy signaling pathway

TABLE 2 Regulation of autophagy by the active compounds of traditional Chinese medicine.

Active compounds of TCM	Chemical structure	Animal type	Dosage and usage	Duration of the study	Behavioral testing evaluation	Antidepressant mechanisms	References
Resveratrol		C57BL/6 mice	30 mg/kg Injected intraperitoneally	21 days	OFT, EPM, FST, SPT, TST	Regulating the activity of SITR1 signaling pathway and regulating the expression of autophagy proteins	Tabassum et al. (2023)
		C57BL/6 mice	20 mg/kg Injected intraperitoneally	28 days	OFT, TST, FST	Stimulating SIRT1, inducing autophagy and inhibiting AKT/mTOR signaling pathway activity	Ye et al. (2023)
Oridonin		Sprague–Dawley rats	5, 10, 20 mg/kg Gavage	6 weeks	SPT, FST	Inhibiting the interaction between NLRP3 and NEK7 to alleviate neuroinflammation and autophagy damage	Liang et al. (2022)
		C57BL/6 mice	20 mg/kg Gavage	14 days	SPT, FST, TST	Activating autophagy to inhibit NLRP3 inflammasome activity	Li et al. (2022c)
Baicalin		C57BL/6 mice	20 mg/kg Gavage	6 weeks	SPT, TST	Activating the AMPK/PGC-1αpathway to enhance NIX mediated mitochondrial autophagy	Jin et al. (2023)
Andrographolide		C57BL/6 mice	2, 5, 5 mg/kg Gavage	46 days	FST, TST, SPT, Y-maze	Activating autophagy to suppress inflammation	Geng et al. (2019)
Allicin		C57 mice	50, 100, 200 mg/kg Gavage	15 weeks	SPT, OFT, TST	Improving mitochondrial function to regulate autophagy, alleviate oxidative stress, and improve NOX/Nrf2 disorder	Gao et al. (2019)

(Continued on following page)

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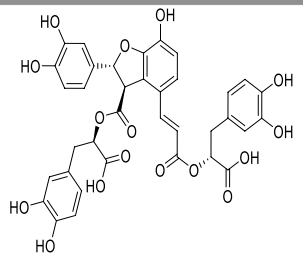
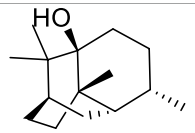
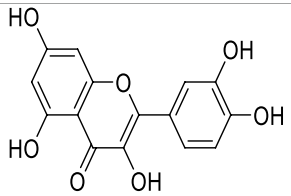
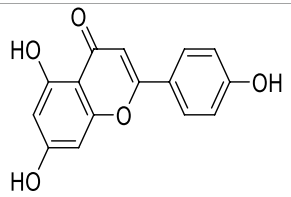
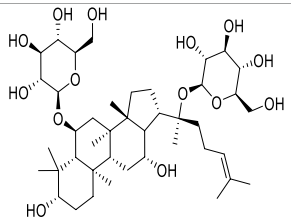
TABLE 2 (*Continued*) Regulation of autophagy by the active compounds of traditional Chinese medicine.

Active compounds of TCM	Chemical structure	Animal type	Dosage and usage	Duration of the study	Behavioral testing evaluation	Antidepressant mechanisms	References
Salvianolic acid B		Sprague–Dawley rats	20 mg/kg Injected intraperitoneally	14 days	FST, SPT, EPM	Promoting autophagy and inducing clearance of NLRP3 inflammasomes	Jiang et al. (2017)
Patchouli alcohol		Sprague–Dawley rats	10, 20, 40 mg/kg Gavage	8 weeks	OFT, SPT, FST	Activating the mTOR signaling pathway to regulate autophagy	Zhuo et al. (2020)
Quercetin		C57BL/6 mice	30, 60 mg/kg Injected intraperitoneally	9 days	TST, FST	Promoting mitochondrial autophagy to inhibit mtROS mediated NLRP3 inflammasome activation in microglia	Han et al. (2021)
Apigenin		BALB/c mice	20, 40, 60 mg/kg Injected intraperitoneally	21 days	SPT, OFT, FST, TST	Acting on the AMPK/mTOR signaling pathway to promote autophagy	Zhang et al. (2019)
Ginsenoside Rg1		Primary astrocytes (Isolation from Sprague Dawley rats)	0.1, 1, 10 μM	Not Applicable	Not Applicable	Regulating the ubiquitin proteasome and autophagy lysosomal degradation pathways of Cx43	Wa et al. (2021)

(Continued on following page)

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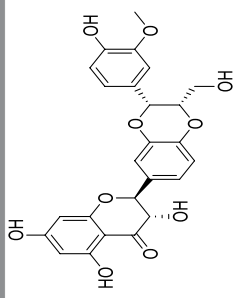
TABLE 2 (*Continued*) Regulation of autophagy by the active compounds of traditional Chinese medicine.

Active compounds of TCM	Chemical structure	Animal type	Dosage and usage	Duration of the study	Behavioral testing evaluation	Antidepressant mechanisms	References
Silibinin		Sprague–Dawley rats	25, 50, 100 mg/kg Gavage	15 days	TST, EPM, FST	Relieve neuronal damage and reduce autophagy in the hippocampus through the BDNF/TrkB pathway	Song et al. (2017)

SIRT1, silent mating-type information regulation 2 homolog 1; AKT/mTOR, adenylate-activated protein kinase/mammalian target of rapamycin; NLRP3, NOD-like receptor pyrin domain containing 3; NEK7, NIMA-related kinase 7; AMPK, adenylate-activated protein kinase; PI3K, Phosphoinositide 3-kinase; Mfn2, mitofusion 2; PGC-1αperoxisome proliferator-activated receptor-gamma coactivator-1α; NIX, Nip-like protein; NOX, NADPH, oxidase; mtROS, mitochondrial reactive oxygen species; Cx43, connexin 43; OFT, open field test; TST, tail suspension test; FST, forced swimming test; SPT, sucrose preference test; EPM, elevated plus maze.

regulation contributes to its antidepressant effect through the integration of network pharmacology and metabolomics (Chi et al., 2022).

Kaixinsan is a TCM compound first proposed by Sun Simiao in the *Tang* Dynasty in the "Golden Prescriptions of the Northern Ages." It is composed of *Polygala tenuifolia*, *Ginseng*, *Poria cocos*, and *Acorus tatarinowii*. Kaixinsan has long been used as a classic formula for treating depression (Wang et al., 2022a; Jiao et al., 2022). Its antidepressant effects have been demonstrated both *in vivo* and *in vitro* by activating autophagy and suppressing NLRP3-mediated inflammation (Yu et al., 2021).

Sinisan, derived from *Zhang Zhongjing*'s treatise on febrile diseases, has been a famous TCM formula for treating depression for thousands of years (Zhang et al., 2023b). It consists of Chaihu (*Radix Bupleuri*), Shaoyao (*Paeonia lactiflora*), Zhiqiao (*Fructus aurantii Immaturus*), and Gancao (*Radix Glycyrrhizae*). Sinisan has been widely used in China to treat liver depression, spleen deficiency, digestive system diseases, and depression (Wang et al., 2022b). Sinisan was shown to prevent excessive autophagy by activating the PI3K/AKT/mTOR pathway, providing a neuroprotective role in a model of CORT-induced neurotoxicity. Thus, it exhibits potential therapeutic effects on depression (Zhang et al., 2021b). The prescription known as Wulingsan, initially documented in the Treatise on Febrile Diseases, has traditionally been employed as a therapeutic intervention for addressing water retention resulting from bladder gasification. This prescription has gained significant popularity in the treatment of ascites (Mou et al., 2022). Studies have found that Wulingsan has obvious antidepressant effects, and its potential mechanism of action involves improving the mitophagy signaling pathway mediated by the 18 kDa translocator protein (TSPO) (Li et al., 2016) (Table 3; Figure 3).

5 Strengths and limitations

MDD is an ongoing challenge in modern medicine since its pathogenesis has not been fully understood and there is still a lack of strategies that can successfully prevent or completely reverse its occurrence (Chen et al., 2022). Autophagy plays a crucial role in MDD, making the regulation of autophagy a potential strategy for the prevention of depression. For the first time, this review provided a comprehensive summary of the mechanisms by which different antidepressant medications, such as fluoxetine, agomelatine, and ketamine, as well as other chemicals, regulate autophagy to treat MDD. However, some antidepressant chemicals that act on the nervous system, such as SSRIs, have been found to have adverse effects such as nausea, headache, chronic sexual dysfunction, and weight gain. Most treatments have delayed effects and high rates of no response (Wang et al., 2019a; Qu et al., 2021; Wei et al., 2022). Ketamine can cause hallucinations, hepatotoxicity, neurotoxicity, addiction, and other side effects, significantly limiting its clinical application. Agomepratine has no significant improvement in the treatment of depression in over one-third of patients (Perrine et al., 2014; Lorman, 2019). At the same time, although chemicals regulating endocrine metabololism such as metformin have been proven to have an antidepressant effect in preclinical and clinical studies. However, there is a risk of increasing the incidence rate of cardiovascular disease, and it will also cause adverse reactions of

TABLE 3 Regulation of autophagy by the antidepressant compounds of traditional Chinese medicine.

TCM compounds	Modeling method	Animal type	Dosage	Duration of the study	Behavioral testing evaluation	Antidepressant mechanisms	References
Xiaoyaosan	CUMS	C57BL/6 mice	0.658 g/kg/d	13 weeks	OFT, SPT, TST	Regulating autophagy and GLUT4 expression in hypothalamic neurons	Yang et al. (2022b)
Modified Xiaoyaosan	CUMS	C57 mice	23 g/kg/d	6 weeks	SPT, TST, OFT, FST	Activate neuronal autophagy to alleviate neuronal damage	Wang et al. (2019b)
Modified Xiaoyaosan	LPS	ICR mice	3.8, 7.6 g/kg/d	16 days	SPT, TST, OFT	Activating the PI3K/Akt/mTOR pathway triggers autophagy to inhibit M1 polarization of microglia and alleviate neuroinflammation	Su et al. (2023)
Mingmu Xiaoyao granule	CUMS	Sprague–Dawley rats	3.8, 7.6 g/kg/d	12 weeks	SPT, OFT	Regulating autophagy through the PI3K/Akt/mTOR signaling pathway	Ma et al. (2022)
Lily bulb and Rehmannia decoction	LPS	Sprague–Dawley rats	90 g/kg	17 days	SPT, FST, EPM	The mechanism of action involves regulation of autophagy pathways	Chi et al. (2022)
KaiXinSan formula	CUMS	Wistar rats	3, 5, 10 g/kg/d	47 days	SPT, OFT, FST	Regulating autophagy to suppress NLRP3 mediated inflammation	Yu et al. (2021)
Sinisan	CORT	Sprague–Dawley rats	0.49 g/mL	Not Applicable	Not Applicable	Activating the PI3K/AKT/mTOR pathway to prevent excessive autophagy	Zhang et al. (2021b)
Wuling powder	IS	ICR mice	0.5, 1, 2 g/kg	2 weeks	NSFT, FST	Regulation of TSPO mediated mitochondrial autophagy signaling pathway	Li et al. (2016)

CUMS, chronic unpredictable mild stress; LPS, lipopolysaccharide; CORT, corticosterone; IS, inescapable e-shock; GLUT4, glucose transporter-4; PI3K/Akt/mTOR, Phosphoinositide 3-kinase/adenylate-activated protein kinase/mammalian target of rapamycin; TSPO:18 kDa translocator protein; OFT, open field test; TST, tail suspension test; FST, forced swimming test; SPT, sucrose preference test; NSFT, Novelty-suppressed feeding test.

digestive system symptoms such as diarrhea and indigestion (Xiao and Luo, 2018).

TCM can regulate autophagy through multiple compounds, targets, and pathways and has great potential in the treatment of MDD. However, most of the current studies on TCM still require further validation through clinical experiments. Many active compounds in TCM have limitations, including poor stability, poor solubility, and difficulty crossing the blood-brain barrier. Additionally, the specific targets of autophagy-related genes in TCM need to be further clarified through mechanistic studies. More importantly, this review highlighted inconsistent findings regarding the inhibition or enhancement of neuronal autophagy, suggesting that the influence of neuronal functional activity during the treatment of depression cannot be disregarded.

Therefore, future research should focus on conducting clinical observations to assess the therapeutic effects and adverse reactions of TCM in MDD patients, as well as investigating the regulatory effect of autophagy in these patients. Moreover, efforts should be made to develop targeted delivery systems for TCM to enhance drug concentration and duration of action in the central nervous system, consequently improving the therapeutic effect of TCM on target organs. Combining multi-omics technology with these studies would further enhance our understanding of the mechanisms and functions of TCM in autophagy regulation, improve our understanding of the pathological mechanisms of autophagy-induced depression, and elucidate the specific roles of neurons and their relationship with autophagy.

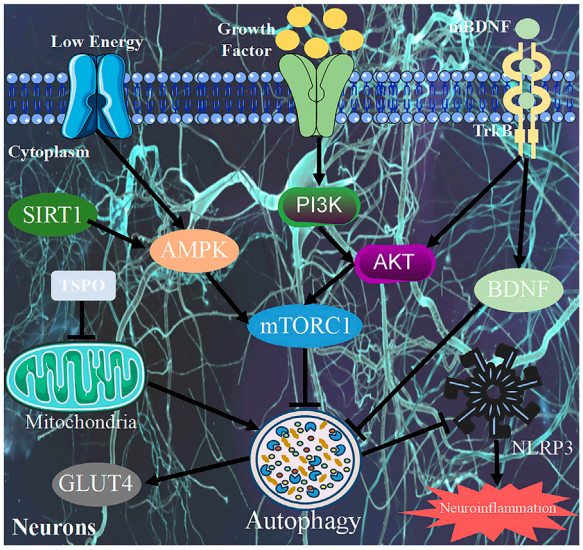


FIGURE 3
Pharmacological mechanism of TCM in regulating autophagy. TCM, Traditional Chinese medicine; mTORC1, mTOR complex 1; BDNF, Brain-derived neurotrophic factor; TrkB, Brain-derived neurotrophic factor-tropomyosin-related kinase B; TSPO, 18 kDa translocator protein; PI3K, Type III Phosphoinositide 3-kinase; AMPK, Adenylate-activated protein kinase; GLUT4, Glucose transporter-4; AKT, Adenylate-activated protein kinase; SIRT1, Silent mating-type information regulation 2 homolog 1.

6 Conclusion

To sum up, autophagy is closely related to the pathological mechanism of MDD. This review further explores the upstream and downstream molecular mechanisms of autophagy affecting MDD, summarizes the relationship between autophagy and MDD related molecular signaling pathways, and further analyzes the pharmacological mechanisms of antidepressants on this basis, in order to provide new strategies for the treatment of MDD patients. However, in both clinical and preclinical studies, more research is needed to explore the mechanisms underlying autophagy regulation by antidepressant agents, which is of great significance for the research and development of TCM in the field of depression therapeutics.

Author contributions

SL: Writing–original draft. GZ: Writing–review and editing. YH: Writing–review and editing. JL: Writing–review and editing. NY: Writing–review and editing. YL: Writing–review and editing. HM: Writing–review and editing. YM: Writing–review and editing. JT: Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Glossary

TCM	Traditional Chinese medicine
MDD	Major depressive disorder
SSRIs	Selective serotonin reuptake inhibitors
5-HT	Serotonin
CMA	Chaperone-mediated autophag
mTORC1	mTOR complex 1
ULK1	Unc51 like autophagy activating kinase 1
PI	Phosphatidylinositol
PI3P	Phosphatidylinositol trisphosphate
PI3K	Type III Phosphoinositide 3-kinase
SNARE	Soluble NSF attachment protein receptor
NLRP3	NOD-like receptor pyrin domain containing 3
IL-1β	Interleukin-1β
HMGB1	High molecular group box 1
STAT3	Signal transducer and activator of transcription 3
NF-κB	Nuclear factor-kappa B
mPFC	Medial prefrontal cortex
NSCs	Neural stem cells
NPCs	Neural progenitor cells
SVZ	Subventricular area
SGZ	Subgranular area
DG	Dentate gyrus
CORT	Corticosterone
ATG	Autophagy-related gene
BDNF	Brain-derived neurotrophic factor
MMP9	Matrix Metalloproteinase 9
AMPK	Adenylate-activated protein kinase
DA	Dopamine
NE	Norepinephrine
E	Epinephrine
Nrf2	Nuclear factor (erythroid derived 2)-like 2
LPS	Lipopolysaccharide
PPD	*Postartum* depression
Gαi-2	G alphai (2)
PKA	Protein kinase A
ASK1	Apoptosis signal-regulating kinase 1
NMDAR	N-methyl-D-aspartate receptor
RAGE	advanced glycation end products
CUMS	Chronic unexpected mild stress
TZD	Thiazolidinedione
H2S	Hydrogen sulfide
SIRT1	Silent mating-type information regulation 2 homolog 1
TrkB	Brain-derived neurotrophic factor-tropomyosin-related kinase B
PDE4	Phosphodiesterase-4
COPD	Chronic obstructive pulmonary disease
DHA	Docosahexaenoic acid
FOXO	Forkhead box o
VE	Vitamin E
NEK7	NIMA-related kinase 7
AMPARs	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)-type glutamate receptor
NIX	Nip-like protein
PGC	Peroxisome proliferator-activated receptor-gamma coactivator
Mfn2	Mitofusion 2
ER	Endoplasmic reticulum
mtROS	mitochondrial reactive oxygen species
Cx43	Connexin 43
XYS	Xiaoyaosan
GLUT4	Glucose transporter-4
TSPO	18 kDa translocator protein
AKT	Adenylate-activated protein kinase

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EDITED BY
Magdalena Sowa-Kucma,
University of Rzeszow, Poland

REVIEWED BY
Shanqiang Qu,
Nanfang Hospital, Southern Medical University, China
Patrycja Pańczyszyn-Trzewik,
University of Rzeszow, Poland

*CORRESPONDENCE
Jing Teng,
60170099@sdutcm.edu.cn

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Ferroptosis: a new antidepressant pharmacological mechanism

Guangheng Zhang[1], Shimeng Lv[1], Xia Zhong[1], Xiangyu Li[2], Yunhao Yi[3], Yitong Lu[1], Wei Yan[4], Jiamin Li[4] and Jing Teng[1]*

[1]Department of First Clinical Medical College, Shandong University of Traditional Chinese Medicine, Jinan, China, [2]Wangjing Hospital, China Academy of Chinese Medical Sciences, Beijing, China, [3]College of Traditional Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan, China, [4]Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, China

The incidence rate of depression, a mental disorder, is steadily increasing and has the potential to become a major global disability factor. Given the complex pathological mechanisms involved in depression, the use of conventional antidepressants may lead to severe complications due to their side effects. Hence, there is a critical need to explore the development of novel antidepressants. Ferroptosis, a newly recognized form of cell death, has been found to be closely linked to the onset of depression. Several studies have indicated that certain active ingredients can ameliorate depression by modulating the ferroptosis signaling pathway. Notably, traditional Chinese medicine (TCM) active ingredients and TCM prescriptions have demonstrated promising antidepressant effects in previous investigations owing to their unique advantages in antidepressant therapy. Building upon these findings, our objective was to review recent relevant research and provide new insights and directions for the development and application of innovative antidepressant strategies.

KEYWORDS

ferroptosis, depression, traditional Chinese medicine, pharmacological mechanism, antidepressants

1 Introduction

Major depressive disorder (MDD), commonly known as depression, is a prevalent mental disorder that poses a significant threat to both physical and mental wellbeing. Its primary clinical manifestations include persistent emotional depression, reduced interest, intellectual disability, cognitive impairment, sleep disturbances, and other psychiatric symptoms. In severe cases, it can even lead to suicidal tendencies (JIAO et al., 2021). The World Health Organization (WHO) predicts that by 2030, depression will be the leading cause of disability worldwide (BARNETT, 2019). Currently, selective serotonin reuptake inhibitors (SSRIs) and other medications are primarily used for treatment. SSRIs selectively inhibit serotonin (5-HT) transporters and block the reuptake of 5-HT, thereby enhancing its effect and producing antidepressant effects (KRAUS et al., 2017). However, these treatments are often associated with adverse reactions such as nausea, headaches, sexual dysfunction, and weight gain. Furthermore, they exhibit delayed efficacy and high non-response rates (WU S. et al., 2021). Consequently, there is an urgent need to develop more effective and safer antidepressant treatments. Traditional Chinese medicine (TCM) possesses characteristics such as multi-component, multi-target, and multi-channel effects, making it a promising approach for depression treatment. Some active ingredients derived from TCM have demonstrated significant antidepressant efficacy without notable toxic side effects

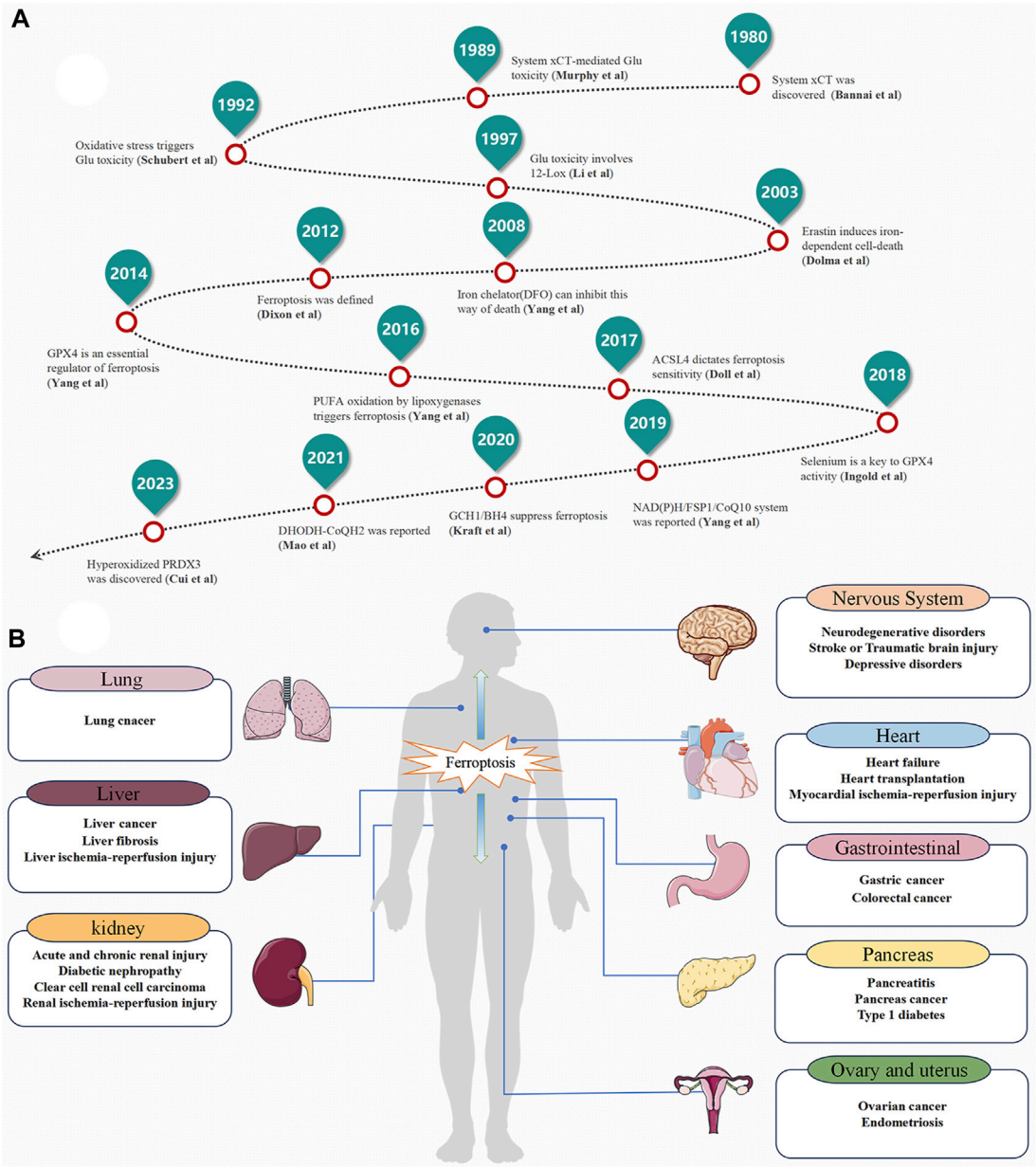


FIGURE 1
The Development History and Distribution of ferroptosis. **(A)** The Development History. **(B)** The Distribution of ferroptosis in the Human Body.

(CHI et al., 2019), providing extensive research opportunities in the field of antidepressant therapy.

Despite advancements, the precise pathological mechanism underlying depression remains incompletely understood (DEAN and KESHAVAN, 2017). Ferroptosis, a newly discovered form of programmed cell death first proposed in 2012, has gained considerable attention in recent years. Iron, as the most abundant transition metal element in the brain, plays a crucial role in various physiological processes, including myelin formation, neurotransmitter synthesis and transmission, and oxidative metabolism of nerve cells (LEI et al., 2021). Consequently, the brain is highly vulnerable to alterations in iron homeostasis (FERREIRA et al., 2019). Disruptions in iron homeostasis can lead to neuronal damage (MAHER, 2018), which is closely associated with the onset of various neurodegenerative diseases, such as Parkinson's and Alzheimer's disease (MAHONEY-SÁNCHEZ et al., 2021). Emerging studies have indicated a correlation between depression and excessive accumulation of iron ions in the brain. Consequently, exploring the regulation of ferroptosis as a potential therapeutic approach for depression holds significant promise for future drug research and development (DUAN et al., 2022).

In this comprehensive review, we searched for recent studies on depression and ferroptosis. PubMed, EMBASE, and MEDLINE scientific databases were searched individually and/or in combination using the following keywords: ferroptosis,

TABLE 1 The main morphological, biochemical, inducing factors and immune features of ferroptosis, apoptosis, autophagy and necroptosis.

	Ferroptosis	Apoptosis	Autophagy	Necroptosis
Morphological features	Significant ultrastructural changes mainly: mitochondrial crumpling, increased density of the bilayer membrane, rupture of the outer membrane, reduction or disappearance of the mitochondrial ridge (LI et al., 2020)	Cell membranes are vacuolated, nuclei are ruptured and crumpled, chromosomes condense, cell size decreases, and apoptotic vesicles form (LI et al., 2020)	Autophagic lysosome formation, cytoplasmic vesicularization (LI et al., 2020)	Cell membrane rupture, cytoplasmic and organelle swelling, cytoplasmic content efflux, chromatin condensation (LI et al., 2020)
Biochemical features	Iron accumulation, lipid peroxidation, decreased cystine uptake, decreased glutathione, increased NAPDH oxidation, release of arachidonic acid mediators, loss of mitochondrial membrane potential (XIE et al., 2016; LI et al., 2020)	Caspases activated, DNA fragmented, mitochondrial membrane potential reduced or absent, PS exposed (XIE et al., 2016; LI et al., 2020)	LC3-I is converted to LC3-II and autophagy substrates (e.g., p62) are catabolized (XIE et al., 2016; LI et al., 2020)	Decreased ATP levels, activation of RIP1, RIP3, and MLKL, release of DAMPs, and PARP1 hyperactivation (XIE et al., 2016; LI et al., 2020)
Inducing factors	Fe2+ accumulation, fatty acid enzyme catalysis	Normal gene regulation under physiological conditions	Lack of nutrition, microbial infections, organelle damageetc.	Severe pathologic injury
Immune features	Release of DAMPs pro-inflammatory (XIE et al., 2016)	Usually anti-inflammatory (XIE et al., 2016)	Usually anti-inflammatory (XIE et al., 2016)	Usually releases DAMPs pro-inflammatory (XIE et al., 2016)

NADPH: Nicotinamide adenine dinucleotide phosphate; Caspases: cysteinyl aspartate specific proteinase; PS: phosphatidylserine; DAMPs: damage associated molecular patterns; LC3-I: microtubule-associated proteins light chain 3-I; LC3-II: microtubule-associated proteins light chain 3-II; p62: prostacyclin-62; ATP: Adenosine triphosphate; RIP1: receptor-interacting protein 1; RIP3: receptor-interacting protein 3; MLKL: mixed-lineage kinase domain-like; PARP1: poly ADP-ribose polymerase-1.

depression, iron, antidepressants, mechanism. The original scientific papers, clinical trials, meta-analyses, and reviews written in English and published up to November 2023 addressing the above topics were enrolled. Case reports and letters were excluded, and 167 articles were ultimately included in the manuscript for review by reviewing the abstract, and full text. We analyzed the process of ferroptosis, explored the underlying pathological mechanisms of depression, and investigated potential connections between the ferroptosis signaling pathway and depression. Additionally, we reviewed relevant research on the modulation of ferroptosis signaling pathways as a potential approach for developing antidepressant interventions. Our aim was to establish a scientific foundation for future basic research and clinical applications in this field.

2 Overview of ferroptosis

Ferroptosis is a form of cell death triggered by the excessive accumulation of iron-dependent lipid peroxides (LI et al., 2020). As early as 2003, Sonam Dolma discovered that erastin induced a novel form of cell death (DOLMA et al., 2003). In 2008, Wan Seok Yang and Brent R. Stockwell found that this type of cell death can be inhibited by iron-chelating agents (DFOM) and vitamin E (YANG and STOCKWELL, 2008). Later, in 2012, Brent R. Stockwell officially named this new form of cell death "ferroptosis" (Figure 1A). Notably, ferroptosis exhibits distinct characteristics in terms of cell morphology and biochemical indicators compared to other forms of regulated cell death (RCD). Unlike apoptosis, ferroptosis does not involve apoptotic bodies, cell shrinkage, or chromatin aggregation. Instead, it is characterized by reduced or vanished mitochondrial ridges, decreased cellular volume, and outer membrane rupture (DIXON et al., 2012; XIE et al., 2016). These unique features distinguish ferroptosis from known forms of cell death (Table 1). Over the past decade, significant progress has been made in the study of ferroptosis, establishing it as a field with great potential for development. Since ferroptosis can lead to damage and degenerative changes in various target organs, regulating ferroptosis signaling pathways holds great significance for improving related diseases (Figure 1B).

3 Mechanism of ferroptosis

Ferroptosis primarily arises from the excessive accumulation of lipid reactive oxygen species (ROS) on the cell membrane due to intracellular metabolic dysregulation. Lipid peroxides and their secondary products, such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), can impair membrane integrity, proteins, and DNA, leading to increased membrane permeability and ultimately triggering ferroptosis (CAPELLETTI et al., 2020). The excessive accumulation of lipid peroxides can occur through two main mechanisms: enzymatic and non-enzymatic pathways (BATTAGLIA et al., 2020). The enzymatic mechanism involves the conversion of polyunsaturated fatty acids (PUFAs) into active lipid peroxides catalyzed by fatty acid enzymes. The other mechanism is attributed to iron metabolism disorders leading to the Fenton reaction. In recent years, additional pathways and targets related to ferroptosis have been identified, expanding the complexity of the regulatory mechanisms involving various signaling molecules and metabolic pathways.

The lipid metabolism pathway catalyzed by lipoxygenases (LOXs) is the primary enzymatic mechanism involved in promoting ferroptosis. Various sources of PUFAs undergo conversion into

PUFA-CoA through acyl CoA synthase 4 (ACSL4). Subsequently, under the catalysis of lysophosphatidyltransferase 3 (LPCAT3), they are transformed into PUFA - phosphatidylethanolamine (PE) (PUFA-PE). These molecules are then oxidized by LOXs in the presence of unstable Fe^{2+}, leading to the formation of phospholipid hydroperoxides (PLOOH) and promoting ferroptosis (FENG and STOCKWELL, 2018). In non-enzymatic pathways, the Fenton reaction mediated by Fe^{2+} plays a crucial role. Unstable chelated Fe^{2+} reacts with hydrogen peroxide (H2O2), generating highly reactive hydroxyl radicals (OH•), which then react with PUFAs, resulting in the formation of PLOOH and triggering ferroptosis (FENG and STOCKWELL, 2018).

3.1 Enzymatic mechanisms

3.1.1 Lipid metabolism pathway

Among the enzymatic pathways involved in ferroptosis, LOXs play a paramount role. The three families of lipid oxidase (cyclooxygenases [COX], cytochromes P450 [CYPs], lipoxygenases [LOXs]) can convert free PUFA into lipid oxides, but it is the LOXs family that has the most significant impact on ferroptosis (FENG and STOCKWELL, 2018). LOXs are enzymes containing non-heme iron and exhibit specificity for the oxidation of PUFAs (XIE et al., 2022). Studies have demonstrated that PEs derived from arachidonic acid (AA) and adrenal acid (AdA) serve as crucial substrates for lipid peroxidation in ferroptosis (DOLL et al., 2017; KAGAN et al., 2017).

The process begins with PEs linked to free AA and AdA, which are converted into AA CoA and AdA-CoA through acyl CoA synthase long-chain family 4 (ACSL4). Subsequently, under the catalytic action of lysophosphatidyl acyltransferase member 3 (LPCAT3), AA-PE and AdA-PE are formed. Finally, these compounds are further converted into PLOOH through the combined catalysis of unstable Fe and LOXs, consequently triggering lipid peroxidation and cell ferroptosis (CHEN et al., 2022). Notably, ACSL4 and LPCAT3 play pivotal roles as driving factors for ferroptosis. ACSL4 is considered a sensitive marker for ferroptosis, as cellular ferroptosis can be induced by glutathione peroxidase 4 (GPX4)−/−, while cells with simultaneous knockout of both GPX4 and ACSL4 can survive normally (CAPELLETTI et al., 2020). Nevertheless, there is still ongoing debate regarding the key LOX subtypes driving ferroptosis in this process (FORCINA and DIXON, 2019). Studies have revealed that the LOX-15 complex, in conjunction with PE binding protein 1 (FEBP1), acts as a specific catalyst for AA/AdA-PEs, leading to lipid peroxidation and promoting cell ferroptosis (STOYANOVSKY et al., 2019). Additionally, another study identified edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one, EDA) as an inhibitor of neuronal cell ferroptosis through downregulation of LOX-5 in neurons, thereby facilitating recovery after spinal cord injury (PANG et al., 2022).

Furthermore, investigations have demonstrated that the combination of nicotinamide adenine dinucleotide phosphate (NADPH)-cytochrome P450 reductase (POR) and nicotinamide adenine dinucleotide (NADH)-cytochrome b5 reductase (CYB5R1) allows electrons from NAD(P)H to react with O2, generating H2O2. Ultimately, this leads to the Fenton reaction with free iron ions, indirectly inducing lipid peroxidation and facilitating cell ferroptosis (YAN et al., 2021).

3.1.2 Glutathione (GSH)-GPX4 pathway

The GSH-GPX4 pathway plays a crucial role in inhibiting lipid peroxidation, and the traditional approach to inducing ferroptosis involves inhibiting the synthesis pathway of GSH. In this pathway, GSH serves as a key antioxidant, and its synthesis primarily relies on intracellular cysteine (Cys) uptake through System Xc-. Cys is then reduced to serve as the direct source for GSH. While the System Xc- is considered the main source of Cys (LOU et al., 2022), studies suggest that Cys can also be synthesized through the sulfur transfer pathway when the System Xc- is inhibited (SHIMADA and STOCKWELL, 2015). The System Xc- and sulfur transfer pathway work cooperatively in Cys synthesis (ZHENG and CONRAD, 2020). However, dysregulation of the System Xc- still leads to Cys deficiency and GSH depletion in cells (LI FJ. et al., 2022).

GPX4, the fourth member of the GPX family containing selenium, plays a crucial role in inhibiting lipid peroxidation. GPX4 contains eight nucleophilic amino acids, including selenocysteine (Sec) (SHA et al., 2021), which is essential for its function (LEI et al., 2019). The unique amino acid sequence and structure of GPX4 establish it as a key regulatory factor in inhibiting ferroptosis (TURCHI et al., 2020; WU et al., 2022). Specifically, GPX4 utilizes reduced GSH as a critical substrate to convert GSH into oxidative GSH (GSSG) and PLOOH into fatty alcohols (PLOH), thus inhibiting the process of lipid peroxidation. In the catalytic cycle of GSH-GPX4, the active group -SeH of GPX4 is oxidized to -SeOH by PLOOH. GSH can then reactivate GPX4 by reducing -SeOH, releasing GSSG while maintaining the activity of GPX4 (LI FJ. et al., 2022). Consequently, inhibiting GSH synthesis has been shown in numerous studies to impair the activity of GPX4 (CHEN et al., 2019; YANG et al., 2020; QIN et al., 2021; YANG et al., 2021).

3.1.3 Ferroptosis suppressor protein 1 (FSP1)-Coenzyme Q10 (CoQ10)-NADPH pathway

Alongside the GPX4 pathway, other pathways contribute to ferroptosis inhibition, notably the FSP1-CoQ10-NAD(P)H pathway and the methoxyphenate pathway. Recent studies propose that the FSP1-mediated ferroptosis defense mechanism can function as an independent parallel system (BERSUKER et al., 2019). This mechanism effectively suppresses ferroptosis even in the absence of GPX4 due to genetic deletion. In the FSP1-CoQ10-NADPH pathway, ferroptosis inhibitory protein 1 (FSP1), previously known as flavoprotein apoptosis-inducing factor mitochondrial 2 (AIFM2), acts as a potent ferroptosis inhibitor by reducing coenzyme Q (CoQ10) on the cytoplasmic membrane to panthenol (CoQH2) (SANTORO, 2020). CoQ10 serves as a lipophilic free radical scavenger and antioxidant, protecting the plasma membrane from oxidative damage caused by free radicals. Additionally, CoQ10 acts as a mobile lipid-soluble electron carrier, preserving the normal energy conversion of mitochondrial respiratory chains (SANTORO, 2020).

Nicotinamide adenine dinucleotide phosphate (NADPH), functioning as a dehydrogenase cofactor, is an essential reducing agent for clearing lipid hydroperoxides (STOCKWELL et al., 2017). FSP1 reduces CoQ10 to CoQH2 through NAD(P)H, which directly inhibits lipid peroxidation or indirectly promotes the regeneration of tocopherol free radicals (vitamin E), a natural chain-breaking antioxidant. This process eliminates lipid free radicals, thereby

inhibiting lipid peroxidation (KAGAN et al., 2017). CoQ10 plays a vital role in this pathway, and when CoQ10 synthesis is inhibited, it results in increased lipid peroxidation (SANTORO, 2020). Although the precise source of CoQ10 synthesis remains unclear, most CoQ10 is synthesized within the mitochondria. Recent research identified a mitochondrial defense mechanism against ferroptosis mediated by dihydroorotate dehydrogenase (DHODH). In the absence of GPX4 activity, DHODH upregulates CoQH2 production to inhibit ferroptosis (MAO et al., 2021). Furthermore, studies have revealed that tetrahydrobiopterin (BH4), facilitated by GTP cyclohydrolase 1 (GCH1), effectively inhibits ferroptosis as a free radical scavenger. BH4 can suppress lipid peroxidation by generating CoQH2. Thus, it is plausible that two independent sources of CoQ10 production exist within cells (KRAFT et al., 2020; SANTORO, 2020; SOULA et al., 2020).

3.1.4 Mevalonate (MVA) pathway

The MVA pathway is another important pathway involved in ferroptosis inhibition. It has significant roles in both the FSP1-CoQ10-NAD(P)H pathway and the GSH-GPX4 pathway. The MVA pathway starts with acetyl CoA, which undergoes a series of reductase reactions, including 3-hydroxy-3-methylglutaryl CoA reductase (HMGCR), leading to the production of MVA. Under the action of coenzymes like methylglutarate kinase (MVK), MVA further produces isoamyl pyrophosphate (IPP) (CHEN et al., 2020). IPP is an intermediate molecule in various biomolecules involved in the regulation of ferroptosis (ZHENG and CONRAD, 2020). For example, IPP can generate farnesyl pyrophosphate (FPP) through the activity of phosphofarnesyl synthase. Subsequently, FPP can be converted to squalene by squalene synthase (SQS). Squalene then undergoes cyclization by squalene cyclase to produce cholesterol. However, when SQS is inhibited, FPP bypasses the cholesterol synthesis pathway and instead converts to CoQ10 (CHEN et al., 2020), thereby inhibiting ferroptosis. Studies have demonstrated that FIN56, a known ferroptosis inducer, can activate SQS, leading to reduced CoQ10 synthesis (SHIMADA et al., 2016).

The MVA pathway also plays a crucial role in GPX4 synthesis. In the selenium-containing GPX4 synthesis pathway, the insertion of Sec is essential for GPX4 to exert its antioxidant activity. This process is facilitated by the catalytic integration effect of IPP (WU et al., 2022). FIN56, as a ferroptosis inducer, can inhibit the integration of Sec on the GPX4 catalytic subunit, thereby reducing the expression of GPX4's antioxidant activity (OU et al., 2022).

3.1.5 Glutamine (Gln) metabolism pathway

The Gln metabolism pathway is another important pathway involved in the regulation of ferroptosis. Gln, a key amino acid in the human body, plays a crucial role in various biological processes and energy production within mitochondria, such as the tricarboxylic acid (TCA) cycle (KOPPULA et al., 2021). Gln is primarily taken up by cells through SLC1A5 and is then broken down by glutaminase (GLS) into glutamic acid. The converted glutamic acid enters the TCA cycle as α-ketoglutaric acid (α-KG) with the help of enzymes like glutamate (GLU) dehydrogenase (GLUD1) (LI S. et al., 2023), regulating lipid synthesis and the ferroptosis process (YAO et al., 2021). GLS, a key enzyme in Gln breakdown, consists of two subtypes: GLS1 and GLS2. Studies have demonstrated that GLS2 is the essential subtype for mitochondrial regulation of ferroptosis (GAO et al., 2015; SUZUKI et al., 2022). GLS2 facilitates the production of glutamic acid, which enters mitochondria and is further converted to α-KG by aspartate aminotransferase (GOT) and GLUD1. This process maintains energy metabolism and component transformation in the TCA cycle (YAO et al., 2021). The glutamic acid derived from Gln breakdown in the TCA cycle induces structural and functional changes in mitochondria, including depolarization of the mitochondrial membrane potential and reduced activity of the mitochondrial electron transfer chain. These changes contribute to the accumulation of lipid ROS, ultimately leading to ferroptosis (SONG et al., 2023). Therefore, modulation of the Gln metabolism pathway can regulate the sensitivity of cells to ferroptosis (KANG et al., 2019; SUZUKI et al., 2022).

Downregulation of solute carrier family 7 member 11 (SLC7A11), a component of System Xc-, has been shown to induce ferroptosis (CHEN et al., 2021). Recent studies have revealed that increased expression of SLC7A11 in tumor cells leads to excessive cystine uptake for GSH synthesis and loss of GLU (YAO et al., 2021), resulting in an imbalance in the Gln metabolism pathway. By inhibiting SLC7A11 or depriving cells of Cys, the glutamic acid produced from Gln breakdown can bypass System Xc- and enter the TCA cycle, leading to the accumulation of lipid ROS and ultimately triggers ferroptosis. Targeting this pathway provides new potential strategies for cancer treatment based on ferroptosis (KOPPULA et al., 2021).

3.2 Non-enzymatic mechanisms

3.2.1 Disorders of iron ion metabolism

As mentioned previously, ferroptosis is primarily triggered by iron-dependent lipid peroxidation. Iron ions are crucial for human physiological processes. Under normal conditions, systemic iron homeostasis relies on the coordinated expression of transferrin (TF), ferroportin 1 (FPN1), transferrin receptor 1 (TfR1), and liver-produced iron regulatory proteins (ROCHETTE et al., 2022). Two forms of iron ions exist in the human body: Fe^{2+} and Fe^{3+}. When there is an imbalance in iron homeostasis, these ions participate in oxidation-reduction reactions, resulting in the production of peroxy free radicals and ultimately leading to ferroptosis (LOU et al., 2022).

During this process, extracellular Fe^{3+} binds to TF and is recognized by TfR1 before being internalized into the cell. Subsequently, within vesicles, prostate transmembrane epithelial 3 antigen antibody (STEAP3) facilitates the reduction of Fe^{3+} to Fe^{2+}. The transported Fe^{2+} from the vesicles enters the cytoplasm either through divalent metal transporter 1 (DMT1) and zinc iron regulatory protein family 8/14 (ZIP8/14), or it binds to ferritin, storing it in unstable iron pools (LIPs). Free Fe^{2+} in the cytoplasm is susceptible to the Fenton reaction, leading to lipid peroxidation. Additionally, ferritin bound to Fe^{2+} in LIP undergoes autophagic degradation, releasing free Fe^{2+} mediated by nuclear receptor coactivator 4 (NCOA4) upon entering the lysosome (CHEN et al., 2022). This initiates the Fenton reaction and promotes lipid peroxidation. FPN serves as the sole protein responsible for transporting Fe^{2+} out of cells, thereby reducing intracellular Fenton reactions and inhibiting ferroptosis (SUN et al., 2022). Furthermore,

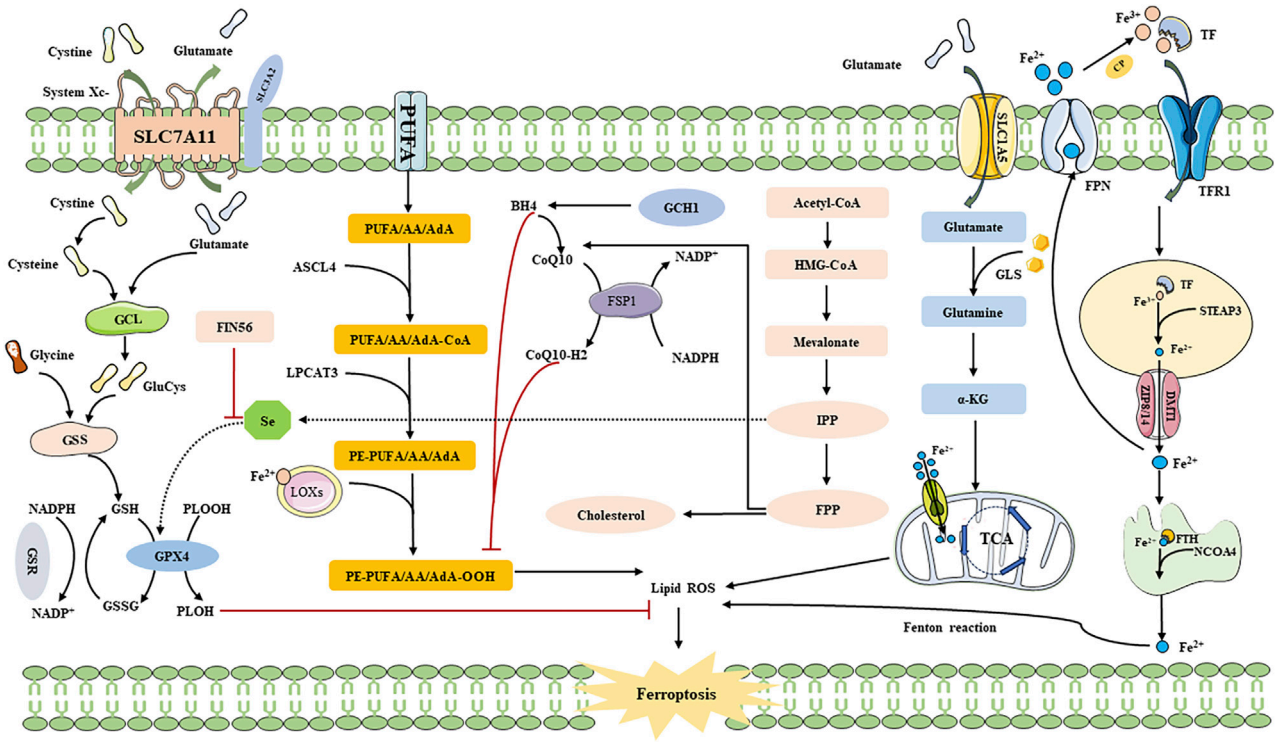


FIGURE 2
The Mechanism of ferroptosis. SLC3A2: solute carrier family 3 member 2; SLC1A5: solute carrier family 1 member 5; SLC7A11: recombinant solute carrier family 7 member 11; GCL: Glutamate-cysteine ligase; GSS: Glutathione synthetase; GSSG: oxidative Glutathione; PLOOH: phospholipid hydroperoxides; PLOH: fatty alcohols; AA: arachidonic acid; AdA: adrenal acid; LOXs: lipoxygenases; CoQ10: Coenzyme Q10; DMT1: Divalent metal transporter 1; Fe^{2+}: Ferrous iron; Fe^{3+}: Ferric iron; FPN: Ferroportin; FSP1: Ferroptosis suppressor protein 1; FTH: Ferritin heavy chain; GSR: Glutathione reductase; GPX4: Glutathione peroxidase 4; GSH: Glutathione; LPCAT3: Lysophosphatidylcholine acyltransferase 3; NCOA4: Nuclear receptor coactivator 4; PUFA: polyunsaturated fatty acid; ROS: Reactive oxygen species; TF: Transferrin; GLS: glutaminase; LPCAT3: lysophosphatidylcholine acyltransferase 3; TfR1: transferrin receptor 1; TCA: citric acid cycle; α-KG: α-ketoglutarate; NADPH: nicotinamide adenine dinucleotide phosphate; CoQ10H2: ubiquinol; GCH1: guanosine triphosphate cyclohydrolase 1; STEAP3: six-transmembrane epithelial antigen of prostate 3; ZIP8/14: zinc iron regulatory protein family 8/14; ACSL4: acyl-CoA synthetase long-chain family member 4; FIN56: ferroptosis inducer; Se: Selenium; HMG-CoA: 3-Hydroxy-3-Methyl-Glutaryl-CoA; IPP: isoamyl pyrophosphate; FPP: farnesyl pyrophosphate.

studies have shown that Fe^{2+} exported via FPN can be converted to less oxidizing Fe^{3+} through the action of ceruloplasmin (CP). Depletion of CP leads to the accumulation of intracellular Fe^{2+}, thus inducing ferroptosis (SHANG et al., 2020).

Moreover, unstable iron within LIP can bind to ferritin (including both ferritin light chain and ferritin heavy chain) and transform into Fe^{3+} for storage in lysosomes, effectively inhibiting lipid peroxidation. In instances of iron deficiency, iron bound to ferritin heavy chain (FTH) can be released into LIP with the aid of NCOA4. Free Fe^{2+} within LIP is crucial for mitochondrial function (FUJIMAKI et al., 2019). The influx of Fe^{2+} from unstable iron pools into mitochondria not only triggers the Fenton reaction leading to ferroptosis, but also serves as a substrate for Fe-S cluster synthesis. The stability of Fe-S clusters plays an indispensable role in maintaining the normal functioning of electron transfer chains (ETC.) and the TCA cycle (FANG et al., 2023). Damage to, ETC can also result in lipid peroxidation and subsequent ferroptosis within cells (JAVADOV, 2022; DONG et al., 2023).

3.2.2 System Xc-pathway

The System Xc-pathway is facilitated by a chloride ion-dependent Glu/Cys transporter protein located on the plasma membrane. This protein consists of solute carrier family 7 member 11 (SLC7A11) and solute carrier family 3 member 2 (SLC3A2), which are interconnected by disulfide bonds (LI FJ. et al., 2022). System Xc-operates based on a concentration gradient of Glu/Cys both inside and outside the cell, allowing for Cys intake into the cell in a 1:1 ratio while Glu is excreted (ISHII et al., 1987; CONRAD and SATO, 2012; LI et al., 2020; WU X. et al., 2021). Several biomolecular synthesis processes occur following the uptake of Cys via System Xc-, leading to the synthesis of GSH. In this process, ingested Cys is catalyzed by thioredoxin reductase 1 (TrxR1) to convert it to Cys, which is then combined with glutamic acid (Glu) through the catalytic action of GLU Cys ligase (GCL) to form γ-glutacyl-L-Cys. Ultimately, this compound is directly utilized in the biosynthesis of GSH along with glycine, thereby inhibiting ferroptosis (LIN et al., 2020; LI FJ. et al., 2022; LIU et al., 2022). Among these steps, the transport of Cys through the amino acid transport system is primarily regulated by SLC7A11 (LI FJ. et al., 2022). Thus, inhibiting the expression of SLC7A11 can increase cellular sensitivity to ferroptosis (JENNIS et al., 2016; NISHIZAWA et al., 2020; WANG et al., 2020). Intracellular Cys can also be acquired through the sulfur transfer pathway and neutral amino acid transporters (CONRAD and SATO, 2012; HAYANO et al., 2016). This indicates that the induction of ferroptosis by

targeting the Cys source is not limited to a singular pathway. However, when ferroptosis inducers like Erastin and its analogues inhibit System Xc- (SATO et al., 2018), intracellular Cys depletion still occurs, leading to reduced GSH synthesis and eventual lipid peroxidation. Therefore, targeting the System Xc-pathway is crucial in modulating GSH synthesis (SHAO et al., 2022) (Figure 2).

4 Depression and ferroptosis

4.1 Iron deposition in depression

Researchers have discovered iron deposition in various individuals with depression, and the dysregulation of iron homeostasis in the brain has been strongly linked to depression (ZHU et al., 2016; WANG et al., 2019; KNYSZYŃSKA et al., 2020; BERTHOU et al., 2021). Initially, different extracellular Fe^{3+} ions are recognized by TfR1 and enter the cytoplasm, where they are then converted into Fe^{2+} under the catalytic influence of STEAP3. Excessive ferrous ions can easily trigger the Fenton reaction, leading to ferroptosis. Therefore, upregulating TfR1 expression increases cellular susceptibility to ferroptosis (YU et al., 2021). Towards the end of the 20th century, a close association between increased TfR1 expression and depression was identified in patients with this condition (MAES et al., 1995a). This suggests that individuals with depression may exhibit a higher propensity for the excessive accumulation of iron ions, resulting in neuronal ferroptosis (MAES et al., 1995b; LIANG et al., 2020). However, some researchers further demonstrated, through a cross-sectional study, that ferroptosis is not related to the severity of depression (ZHANG et al., 2019). Thus, iron deposition in the gray matter of the brain may serve as a potential biomarker for depression (YAO et al., 2017). Moreover, the relationship between depression and iron deposition has also been established through animal experiments. Chang et al., using proteomic techniques, compared the expression differences of TF and TfR1 in the brains and peripheral blood of normal mice and chronic social defeat stress (CSDS)-induced depression mouse models. The results indicated higher expression levels of TF and TfR1 in the peripheral blood and brain of CSDS-induced depression mouse models compared to the control group (CHANG et al., 2022). Further studies have demonstrated a strong correlation between the onset of depression and the reduction of hippocampal neuronal synapses, which is attributed to the upregulation of TfR1 and downregulation of FTL caused by nuclear factor erythroid-2 related factor 2 (Nrf2) deficiency (ZENG et al., 2023). These findings align with the research conducted by Wang et al., whose team elucidated the association between iron deposition in the hippocampus and depression, along with confirming the reduction of FTH induced by lipopolysaccharide (LPS) in depressed mice (WANG et al., 2021a).

4.2 Potential pathologic link between depression and ferroptosis

4.2.1 Iron deposition and neuroinflammation

Neuroinflammation refers to the immune response of the central nervous system (CNS) mediated mainly by microglia and astrocytes in the hippocampus (LEE and HYUN, 2023). Microglia, known for their high iron content (UZUNGIL et al., 2022), have been implicated in depression associated with abnormal glial activation and iron overload, suggesting a potential connection between iron and neuroinflammation (ZENG et al., 2023). However, the precise mechanism by which iron overload disrupts neurotransmitter homeostasis and induces anxiety and depressive behaviors remains unclear (UZUNGIL et al., 2022).

Research has shown that signal transduction involving brain-derived neurotrophic factor (BDNF) plays a crucial role in synaptic plasticity in depression, and the downregulation of BDNF may contribute to neurotoxic effects (SHKUNDIN and HALARIS, 2023). In this context, Li et al. demonstrated that iron overload may downregulate BDNF via the iron urin BDNF pathway, leading to hippocampal nerve damage (LI J. et al., 2023). Furthermore, Gao et al. showed in a chronic unpredictable mild stress (CUMS) mouse model that iron deposition in microglia within the hippocampus is closely associated with neuronal degeneration and death (GAO W. et al., 2019). Additionally, Zeng et al. highlighted the significant role of Nrf2 as an anti-inflammatory factor in regulating iron deposition and neuroinflammatory responses in depression (ZENG et al., 2023). In a comparative study using hippocampal proteomics, Cao et al. observed distinct protein expression differences between normal mice and CUMS model mice, indicating pronounced activation of neuronal necrosis and iron deposition in the hippocampus, thus promoting the occurrence of depression (CAO et al., 2021). Recently, Zhang et al. discovered that expression levels of various inflammatory factors significantly increased in CUMS model mice, while treatment with the iron chelating agent deferoxamine (DFO) effectively reversed this neuropathological change (ZHANG W. et al., 2022). Collectively, these findings suggest a potential link between the neurotoxicity induced by iron overload and the development of depression.

4.2.2 Iron deposition and mitochondrial dysfunction

Since the discovery of ferroptosis in 2012, mitochondria have been proposed to play a crucial role in regulating erastin-induced ferroptosis (FANG et al., 2023). Multiple membrane iron transporters (MFRNs) located on the mitochondrial membrane facilitate the distribution of iron within mitochondria and the cytoplasm. When mitochondrial iron overload occurs, it leads to the generation of a substantial amount of mtROS, resulting in cellular ferroptosis (FUHRMANN and BRÜNE, 2022). Two potential mechanisms for mitochondrial ferroptosis have been suggested (FANG et al., 2023). Firstly, an imbalance in mitochondrial iron homeostasis and an elevation in Fe^{2+} levels promote ROS production via the Fenton reaction, ultimately inducing cell ferroptosis. Secondly, as iron serves as a key regulator of oxidative phosphorylation (OXPHOS), disruption of iron metabolism can lead to impaired electron transfer, lipid peroxidation, and subsequent induction of ferroptosis. Mitochondria contain a significant amount of iron, primarily involved in heme synthesis, Fe-S cluster biosynthesis, and storage within mitochondrial-specific ferritin (FtMt), which maintains the structure and function of the electron transport chain (ETC.) and TCA cycle. Disturbances in iron metabolism can significantly cause structural changes and dysfunction of mitochondria (CHENG et al.,

2022; DONG et al., 2023). ROS produced by mitochondrial dysfunctionis essential for ferroptosis induction (GAO M. et al., 2019). Numerous studies have demonstrated a close association between depression and oxidative stress, as well as disruptions in the, ETC within mitochondria (SONG et al., 2023; XU et al., 2023). In recent years, research has increasingly focused on the mechanism of ferroptosis in patients with depression. Adenosine triphosphate (ATP), predominantly produced by mitochondria, has been found to exhibit a positive correlation with the occurrence of depression (INCZEDY-FARKAS et al., 2014; CHANG et al., 2015; BRYMER et al., 2018; WANG et al., 2018). Kondo et al. further confirmed this relationship using magnetic resonance spectroscopy (MRS) (KONDO et al., 2011). When mitochondrial iron metabolism disorders occur, excessive free iron ions can impair the, ETC and subsequently inhibit ATP production (BATTAGLIA et al., 2020). Romano et al. reviewed the potential role of 4-HNE, a product of ferroptosis (CAPELLETTI et al., 2020), in the pathogenesis of mental disorders such as bipolar disorder and depression, along with lipid peroxidation (ROMANO et al., 2017). Mitochondria, being the primary source of cellular ROS, may also be involved in modulating depression via the ferroptosis signaling pathway (BANSAL and KUHAD, 2016). Based on the available evidence, disturbances in mitochondrial iron metabolism can contribute to the development of depression by influencing mitochondrial function and structure (ZUO et al., 2022; SONG et al., 2023).

4.2.3 Iron deposition and gut flora

The brain-gut axis (GBA) refers to a bidirectional signaling network involving the brain, gut, and gut microbiota. This network operates through neuroendocrine, immune regulation, and microbial molecules, connecting emotional and cognitive activities in the brain with physiological and pathological changes in the peripheral gut (KANIA et al., 2023). The occurrence of depression and bipolar disorder may be associated with intestinal microbiota and dysfunction in the bidirectional communication within the CNS (GÓRALCZYK-BIŃKOWSKA et al., 2022). Remarkably, imbalances in serum iron homeostasis can induce both intestinal microbiota imbalance and inflammation, leading to stress responses in the brain. Consequently, the expression of IL-6 is promoted, which triggers glial cells to release hemodulin, isolating excess iron in neurons. However, this process can unexpectedly induce oxidative stress response, resulting in neuronal damage (HOUSER and TANSEY, 2017; KANIA et al., 2023). Furthermore, studies have elucidated the potential connection between the IL-6-mediated signaling pathway and the pathogenesis of depression (TING et al., 2020). Additionally, as previously mentioned, iron overload may contribute to depression by downregulating the expression of BDNF (LI J. et al., 2023; SHKUNDIN and HALARIS, 2023). Recent research has demonstrated that alterations in gut microbiota distribution, according to the brain-gut axis mechanism, can modulate BDNF expression, thereby influencing the onset of depression (LIAQAT et al., 2022). Moreover, a meta-analysis revealed decreased levels of *Corprococcus* and *Faecalibacterium* bacteria in the intestines of individuals with depression compared to healthy individuals. Notably, intervention with probiotics resulted in improved depression symptoms. Taken together, these findings suggest that ferroptosis may inhibit the damage caused by neuroinflammation through cross talk among the brain-gut axis mechanism, gut microbiota, and CNS (WANG et al., 2023a; KANIA et al., 2023). Thus, it holds promise as a potential target for the diagnosis and treatment of depression.

4.2.4 Iron deposition and autophagy

Autophagy is a natural and RCD process that facilitates the degradation of damaged organelles, pathogens, and other biological components (such as proteins, lipids, DNA, and RNA) within cells. It serves as a survival mechanism in response to stress (LIU et al., 2020). The relationship between autophagy and ferroptosis remains unclear. Recent studies have proposed that ROS triggered by the ferroptosis inducer erastin can induce autophagy in cells, and autophagy, in turn, can regulate ferroptosis by degrading cellular ferritin (PARK and CHUNG, 2019). Zuo et al. demonstrated that oxidative stress, mediated by ROS, plays a crucial role in depression induction, and Nrf2 activation can mitigate oxidative stress by simultaneously regulating multiple potential mechanisms, including autophagy and ferroptosis (ZUO et al., 2022). Furthermore, mitochondrial autophagy has been found to be significant in depression (TRIPATHI et al., 2021), and Nrf2 activation can directly modulate mitochondrial autophagy (MURATA et al., 2015). From the perspective of ferroptosis, the ferroptosis pathway may also hold promise as a potential mechanism for treating depression (ZUO et al., 2022). Autopsy results from patients with depression revealed decreased levels of GSH and GPX in the brain (GAWRYLUK et al., 2011). Wigner et al. identified a potential association between GPX4 gene polymorphism and depression regulation (WIGNER et al., 2018). Additionally, it has been demonstrated that most genes involved in ferroptosis are directly or indirectly regulated by Nrf2 (HARADA et al., 2011; DODSON et al., 2019). Dang et al. investigated the effects of EDA and showed its ability to reduce oxidative stress and ferroptosis through the Silent information regulatory factor 2 homologous protein 1 (Sirt1)/Nrf2/Heme oxygenase-1 (HO-1)/Gpx4 pathway, thereby inhibiting the development of depression (DANG et al., 2022). These findings provide evidence of crosstalk between autophagy and ferroptosis in the pathological mechanism of depression, which may serve as a potential therapeutic avenue for depression.

5 Treating depression by inhibiting ferroptosis

5.1 Traditional Chinese medicine

5.1.1 Active ingredients of traditional Chinese medicine

Allicin, a prominent active compound in Chinese herbal garlic, has been found to possess neuroprotective effects (CHEN et al., 2014). Gao et al. demonstrated that Allicin can alleviate depressive behavior in the CSDS model mice by inhibiting NLRP3 inflammasomes. Increased concentration of DMT1 in hippocampal neurons during the chronic phase of inflammation indicates iron deposition, suggesting a potential link between Allicin and ferroptosis as one of the mechanisms for treating depression (GAO W. et al., 2019).

Saikosaponin B2 (SSB2), derived from the Chinese herbal medicine Radix Bupleuri, has a long history of being used to treat depression, as documented in the TCM classic "*Taiping Huimin HeJiJu Fang*" (YANG et al., 2017). The antidepressant and neuroprotective effects of Radix Bupleuri have been confirmed through modern research (TONG et al., 2024). Wang et al., using the CUMS mouse model and ferroptosis mouse model, demonstrated that SSB2 inhibits Toll-like receptor 4 (TLR4)/nuclear factor kappa-B (NF-κB) pathway-mediated ferroptosis to improve depression-induced microglia activation. This leads to inhibition of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α. However, the therapeutic effect of SSB2 on depression is blocked when GPX4 is knocked out, indicating that SSB2 acts through a GPX4-dependent manner in mediating TLR4/NF-κB pathway, exerting its anti-ferroptosis and anti-neuroinflammatory roles (WANG et al., 2023b).

Lycium barbarum glycopeptide (LbGp), a carbohydrate conjugate composed of proteins and monosaccharides, is a major active component of Chinese herbal medicine *Lycium barbarum* (PENG et al., 2001). Recent studies have shown that goji berry polysaccharides effectively alleviate depression (FU et al., 2021; LI X. et al., 2022). Dai et al. observed in their study using chronic restraint stress (CRS) model mice that GPX4 knockout-induced ferroptosis disrupts cortical function, leading to increased depression and anxiety in mice. However, treatment with LbGp can attenuate the anxiety caused by ferroptosis by increasing superoxide dismutase (SOD) activity and inhibiting the elevation of GSH and MDA levels (DAI et al., 2023). Gallic acid (3,4,5-trihydroxybenzoic acid) is an active ingredient extracted from Chinese herbal medicine found in various plants, such as green tea and gallnuts (Al Zahrani et al., 2020). Recent studies have revealed that the phenolic hydroxyl group of gallic acid has the ability to clear ROS and disrupt the cycle of new free radicals, thereby exhibiting anti-inflammatory properties (TEIXEIRA et al., 2013). Yang et al. discovered that gallic acid can effectively treat depression development by inhibiting the P2X7 regulatory ferroptosis signaling pathway in chronic contractile injury (CCI) model rats and CUMS model rats. Inhibition of P2X7 expression leads to downregulation of TNF-α, NF-κB expression levels, and STAT3 phosphorylation. Consequently, the expression of GSH and GPX4 increases, which suppresses ROS accumulation and the generation of MDA, ultimately alleviating the pain and depressive symptoms in CCI and CUMS rats through the inhibition of ferroptosis (YANG R. et al., 2023). Silybin, another primary active ingredient derived from Chinese herbal medicine Silybin, has been shown to possess neuroprotective effects as well as antidepressant effects (SONG et al., 2018; LIU et al., 2021). Liu et al. discovered that silybin reduces neuroinflammation mediated by interferon gene stimulating factor (STING) by downregulating the ferroptosis signaling pathway. This leads to an improvement in depressive behavior in an Alzheimer's disease mouse model. Hippocampal neurons (HT-22) treated with streptozotocin (STZ) exhibit dysregulation of the p53/SLC7A11/GSH/GPX4 pathway, resulting in excessive ROS accumulation and ferroptosis activation, which subsequently triggers the cellular immune response via the STING signaling pathway. This pathological mechanism induces the release of various inflammatory factors, leading to depressive behavior in mice. Silybin treatment can reverse this pathological change by inhibiting the ferroptosis signaling pathway (LIU et al., 2023) (Table 2).

5.1.2 TCM compounds

Currently, there is limited research on the modulation of the ferroptosis signaling pathway in TCM prescriptions for treating depression. Recent studies employing metabolomics and nuclear MRS have revealed the potential antidepressant effects of Xiaoyao powder (consisting of *Radix Bupleuri*, *Poria*, *Rhizoma Zingiberis Recens*, *Radix Angelicae Sinensis*, *Radix* Paeoniae Alba, *Rhizoma Atractylodis Macrocephalae*, *Radix Glycyrrhizae*, and *Herba Menthae Haplocalycis*) on CUMS rats (LIU et al., 2019). Jiao et al. found that Xiaoyao powder ameliorates depression-like behavior in CUMS model mice by modulating the ferroptosis signaling pathway mediated by the hippocampus. The antidepressant mechanism of Xiaoyao powder may involve the upregulated expressionsof PEBP1 and extracellular regulatory protein kinase 1/2 (ERK1/2), and modulation of GPX4 within the ferroptosis signaling pathway. These findings suggest that Xiaoyao powder may alleviate depressive behavior in mice through mediating PEBP1-GPX4 interactions (JIAO et al., 2021).

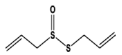
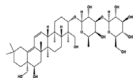
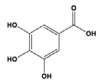
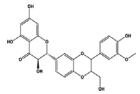
Furthermore, Dihuang Yinzi (composed of *Radix Rehmanniae* Praeparata, *Radix Ophiopogonis*, *Caulis Dendrobii*, *Fructus Corni*, *Fructus Schisandrae Chinensis*, *Herba Cistanches*, *Radix Morindae Officinalis*, *Radix Aconiti Lateralis Praeparata*, *Cortex Cinnamomi*, *Poria*, *Rhizoma Acori Tatarinowi*i, *Radix Dolygalae*, *Herba Menthae*, *Rhizoma Zingiberis Recens*, and *Fructus Jujubae*) has been found to possess neuroprotective effects (ZHANG et al., 2017). Moreover, Zhou et al. observed that Dihuang Yinzi can mitigate neural damage caused by post-stroke depression (PSD) in rats by regulating the ferroptosis signaling pathway. The active extract of Dihuang Yinzi modulates the P53/SLC7A11 pathway and upregulates the expression of SLC7A11 protein through promotion of P53 ubiquitination, consequently increasing GPX4 expression. This intervention effectively inhibits ferroptosis in PSD, improving depressive symptoms and cognitive impairment (YANG Z. et al., 2023).

5.2 Chemicals with antidepressant effects

In addition to extracts and active ingredients from TCM compounds, several other chemicals have shown potential in regulating ferroptosis pathways to ameliorate depression (WANG et al., 2021b; DANG et al., 2022; UZUNGIL et al., 2022; Wang et al., 2022; Zhang et al., 2022; Li et al., 2023). Deferiprone (DFP), a commonly used iron chelating agent, demonstrates the ability to cross the blood-brain barrier (BBB) and transfer iron from DFP-Fe to TF for the treatment of serum iron overload. It has been proven effective with low toxicity in improving depressive-like behavior by reducing brain iron levels and tau protein levels (Rao et al., 2020; SUN et al., 2023). Furthermore, Uzungil et al. propose that DFP may exert its antidepressant effect through the lateral amygdala and lateral septum, potentially associated with changes in the unstable iron pool in the brain (UZUNGIL et al., 2022).

Edaravone (EDA) is a highly biologically active free radical scavenger known for its antioxidant, anti-inflammatory, and neuroprotective effects (SRIRAM et al., 2016). It is commonly

TABLE 2 Regulation of ferroptosis by the active compounds of traditional Chinese medicine.

Active compounds of TCM	Chemical structure	Molecular formula	CAS number	Moulding method	Animal or cell type	Dosage of drugs used	Behavioral testing evaluation	Antidepressant mechanisms	References
Allicin		$C_6H_{10}OS_2$	539-86-6	CSDS	C57BL/6J mice, CD-1 mice	2, 10, 50 mg/kg	SPT, FST, SIT	Amelioration of Neuroinflammation, Abnormal Iron Accumulation, Oxidative Stress, and Neuronal Apoptosis via Inhibition of the NLRP3 Pathway in the Hippocampus Ameliorates Depression-Like Behavior	GAO et al. (2019a)
Saikosaponin B2		$C_{42}H_{68}O_{13}$	58,316-41-9	CUMS	ICR mice of SPF grade	5, 10 mg/kg	SPT, OFT, FST	Inhibition of ferroptosis, neuroinflammation via TLR4/NF-κB pathway in a GPX4-dependent manner ameliorates depression	WANG et al. (2023b)
Gallic Acid		$C_7H_6O_5$	149-91-7	CUMS、CCI	Sprague–Dawley rats	100 mg/kg	PBT, SPT, FST, OPT	Modulation of GSH/GPX4 signaling pathway in ferroptosis by inhibition of P2X7 ameliorates depression	YANG et al. (2023a)
Silibinin		$C_{25}H_{22}O_{10}$	802,918-57-6	STZ	Sprague-Dawley rats	25, 50, 100 mg/kg	NORT, EPMT, FST, SPT	Inhibition of STING signaling pathway activation through modulation of p53/SLC7A11/GSH/GPX4 signaling pathway to ameliorate depression	LIU et al. (2023)

CCI: chronic constrictive injury; STZ: streptozotocin; NLRP3: NOD-like receptor pyrin domain-containing 3; NF-Kb: Nuclear factor-kappa B; TLR4: Toll-like receptor 4; SLC7A11: Solute Carrier Family 7 Member 11; PBT: pain behavioral test; SIT: social interaction test; p53: tumor suppressor protein.

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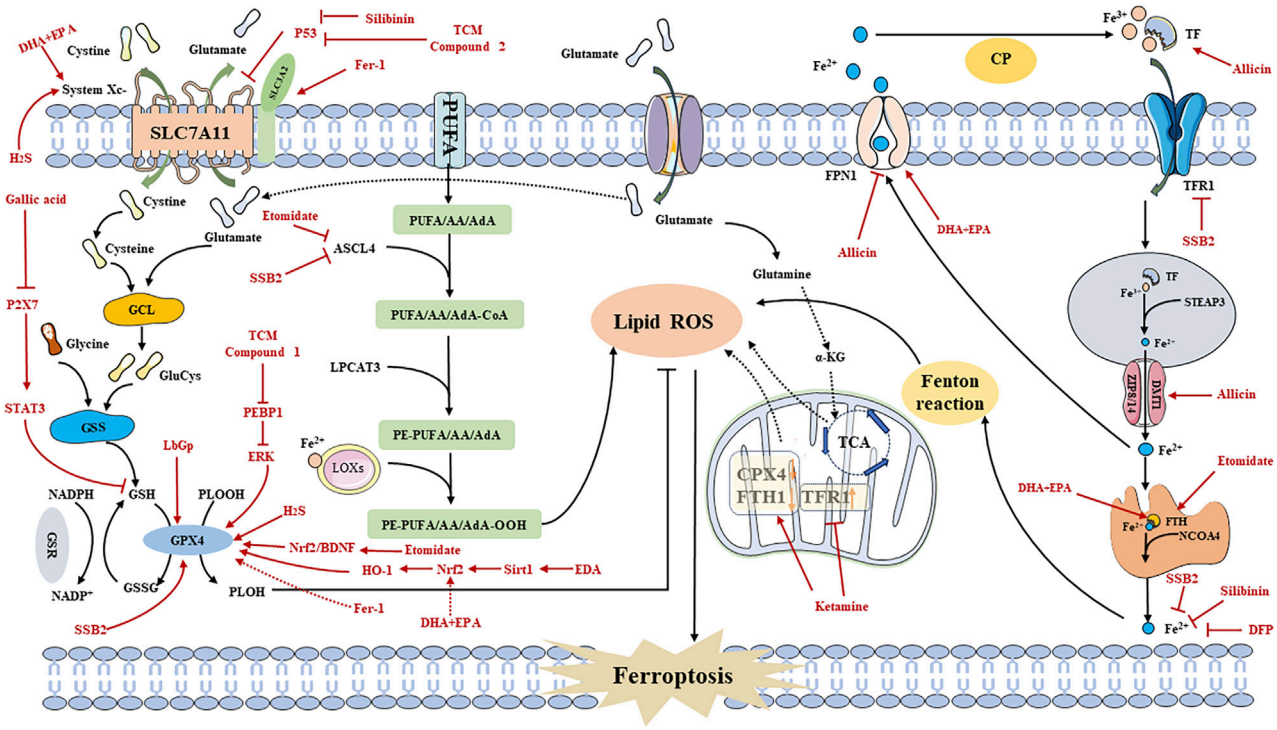


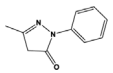
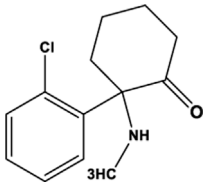
FIGURE 3
Regulating ferroptosis to Treat Depression Mechanisms. Fer-1: ferrostatin-1; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; SSB2: Saikosaponin B2; DFP: Deferiprone; TCM: traditional chinese medicine; PEBP1: Phosphatidylethanolamine Binding Protein 1; EDA: Edaravone; Sirt1: silent mating-type information regulation 2 homolog 1; HO-1: Heme oxygenase-1; Nrf2: Nuclear Factor erythroid 2-Related Factor 2; BDNF: brain-derived neurotrophic factor; EPK: extracellular regulated protein kinases; LbGp: Lycium barbarum glycopeptide; STAT3: signal transducers and activator of transcription 3; H_2S: Hydrogen sulfide; CP: Ceruloplasmin.

used in the treatment of acute cerebrovascular diseases. Studies indicate that EDA may improve corticosterone-induced depression-like behavior in mice by modulating the Fkbp5, Comt, Adora1, and Slc6a15 genes (HERBET et al., 2019). Dang et al. found that EDA can alleviate depression and anxiety-like behavior through the Sirt1/Nrf2/HO-1/Gpx4 pathway using the CSDS mouse model. SIRT1 affects downstream Nrf2. HO-1, a key stress-inducing protein targeted by Nrf2, participates in GPX4 synthesis. Both Nrf2 and HO-1 inhibit ferroptosis and the activation of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α), thereby improving depressive-like behavior (DANG et al., 2022).

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are essential components of Omega-3 PUFAs (n-3-PUFAs), known to improve depression by reducing inflammation and enhancing the expression of neurotrophic factors (PENG et al., 2020). Moreover, a potential association has been found between decreased peripheral blood concentration of n-3-PUFAs, particularly EPA and DHA, and the pathogenesis of depression (Song et al., 2016). Wang et al. conducted a study using the pentylenetetrazole (PTZ) provocation model and found that both DHA and EPA can alleviate depressive behavior in mice by inhibiting ferroptosis and neuroinflammation. Following PTZ treatment, there was a significant increase in the expression of iron regulatory protein (IRP) 1 (IRP1), IRP2, and TfR1 in mice, while FPN1 and FTH1 showed significant reductions. Additionally, Western blot analysis revealed a decrease in the protein expression of GPX4, System Xc-, Nrf2, and HO-1 in mice, but EPA and DHA were able to reverse these pathological changes, mitigating inflammation and iron deposition, and ultimately improving depressive behavior in mice (Wang et al., 2022).

Hydrogen sulfide (H_2S), a gaseous signaling molecule, plays various roles such as neuronal transmission, smooth muscle relaxation, and cell protection against oxidative stress. It is produced by enzymes including β Synthases, Cystine γ Lyase, 3-mercaptopyruvate thiotransferase, and Cys aminotransferase (WU et al., 2018). Recent research has discovered that H2S can inhibit depression-like behavior induced by CRS through upregulation of adiponectin (Q et al., 2018). Furthermore, Wang et al. utilized a model of type 1 diabetes mice induced by STZ to demonstrate that H2S can alleviate depression-like behavior in these mice by inhibiting the inflammatory response and the ferroptosis signaling pathway. In the STZ model, ferroptosis occurs alongside GPX4 inactivation, oxidative stress, and System Xc- inhibition. NaHS, as the primary donor of H2S, can enhance GPX4 activity and increase the expression of SLC7A11 and Cys β-synthase (CBS), thereby reducing the levels of MDA and ROS, ultimately inhibiting ferroptosis. Additionally, NaHS can suppress the inflammatory response by upregulating the expression of sirtuin 6 (Sirt6), leading to reduced acetylation of histone H3 lysine 9 (H3K9) and downregulation of Notch1 expression, thereby inhibiting inflammation. Ultimately, NaHS improves depressive behavior in type 1 diabetes mice by modulating the inflammatory

TABLE 3 Regulation of antidepressant chemicals on ferroptosis.

Antidepressant chemical	Chemical structure	Molecular formula	CAS number	Moulding method	Animal or cell type	Dosage of drugs used	Behavioral testing evaluation	Antidepressant mechanisms	References
Deferiprone		$C_7H_9NO_2$	30,652-11-0	5-HTT KO	C57BL/6Jmice	50 mg/kg/d	PST, Locomotor Activity, NSFT	May potentially modulate unstable iron pools in the brain with amelioration of oxidative stress, thereby improving depressive-like behavior	UZUNGIL et al. (2022)
Edaravone		$C_{10}H_{10}N_2O$	89-25-8	CSDS	C57BL/6J mice、CD-1 mice	10 mg/kg/d	SPT, OPT, EPMT, TST, FST, NORT	Improvement of Depression-like Behavior through Modulation of the Sirt1/Nrf2/HO-1/Gpx4 Signaling Pathway	DANG et al. (2022)
Eicosapentaenoic acid		$C_{20}H_{30}O_2$	32,839-30-8	PTZ	ICR mice	1%,w/w	OFT, FST, TST	Improvement of depression by reversing the expression of transferrin proteins such as TfR1, FPN1 and FTH1 and inhibiting ferroptosis through modulation of the Nrf2/HO-1/System Xc-/GSH/GPX4 signaling pathway	Wang et al. (2022)
Docosahexaenoic acid		$C_{22}H_{32}O_2$	6217-54-5	PTZ	ICR mice	1%,w/w	OFT, FST, TST	Inhibition of ferroptosis and inflammation ameliorates depression by reversing the expression of transferrin proteins such as TfR1, FPN1, and FTH1 and modulating the Nrf2/HO-1/System Xc-/GSH/GPX4 signaling pathway	Wang et al. (2022)
H_2S		H_2S	7783-06-4	STZ	C57BL/6J mice	5.6 mg/kg/d	OFT, EPMT, FST, TST	Improvement of depression through modulation of System Xc-/GSH/GPX4 signaling pathway in ferroptosis, inhibition of pro-inflammatory cytokine release and enhancement of sirtuin 6 (Sirt6) protein expression	WANG et al. (2021b)
Ketamine		$C_{13}H_{16}ClNO$	100,477-72-3	CRS	Wistar-Kyoto (WKY) rats	10 mg/kg	OFT, SPT, FST, TST	Inhibition of ferroptosis by reversing TfR1, FTH1 and GPX4 expression ameliorates depression	Zhang et al. (2022)

(Continued on following page)

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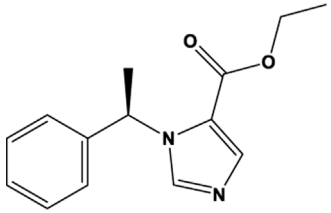
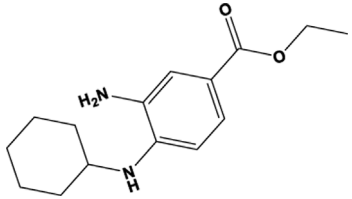
TABLE 3 (*Continued*) Regulation of antidepressant chemicals on ferroptosis.

Antidepressant chemical	Chemical structure	Molecular formula	CAS number	Moulding method	Animal or cell type	Dosage of drugs used	Behavioral testing evaluation	Antidepressant mechanisms	References
Etomidate		$C_{14}H_{16}N_2O_2$	33,125-97-2	CUMS	Sprague-Dawley rats	20 mg/kg	OFT, SPT, FST	Inhibition of ferroptosis through modulation of GSH/GPX4 signaling pathway, lipid metabolism pathway, and expression of transferrin FTH in ferroptosis ameliorates depression	Li et al. (2023)
Ferrostatin-1		$C_{15}H_{22}N_2O_2$	347,174-05-4	CUMS	Sprague-Dawley rats	2 mg/kg	OFT, SPT, FST	Inhibition of ferroptosis through modulation of System Xc-/GSH/GPX4 signaling pathway in ferroptosis ameliorates depression	Li et al. (2023)
				CORT, CUMS	C57BL/6 mice	5 mg/kg	SPT, OPT, TST, FST	Inhibition of ferroptosis and promotion of CORT-induced cell regeneration in neuronal cells by downregulation of tsRNA-3029b ameliorates depression	LONG et al. (2023)

5-HTT KO: serotonin transporter knockout; CUMS: chronic unpredictable mild stress; CRS: chronic restraint stress; CSDS: chronic social defeat stress; CRS: chronic restraint stress; CORT: corticosterone; STZ: streptozotocin; PTZ: pentylenetetrazole; OFT: open field test; TST: tail suspension test; FST: forced swimming test; SPT: sucrose preference test; EPMT: elevated plus maze test; NSFT: novelty-suppressed feeding test; NORT: novel object recognition test; Nrf2: nuclear factor (erythroid-derived 2)-like 2; SIRT1: silent mating-type information regulation 2 homolog 1; GSH: glutathione; GPX4: glutathione peroxidase 4; System Xc-: cystine/glutamate transporter; HO-1:Heme oxygenase-1; TfR1: transferrin receptor 1; FTH1: Ferritin Heavy Chain 1; FPN1: ferroportin 1.

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response and the ferroptosis signaling pathway and their correlation (WANG et al., 2021b).

Ketamine (non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors) is a racemic compound consisting of equal amounts of R-ketamine and Esketamine. Esketamine has demonstrated clear antidepressant effects, and its nasal spray has been approved by the United States and Europe as an adjunctive therapy to oral antidepressants for treatment-resistant depression (TRD) in adults (Jelen et al., 2021). Studies have suggested that the antidepressant properties of ketamine may be associated with downstream mechanisms involved in regulating synaptic plasticity, including brain-derived neurotrophic factor (BDNF), eukaryotic elongation factor 2 kinase (eEF2K), mechanistic target of rapamycin (mTOR), and glycogen synthase kinase-3 (GSK-3) (ZANOS and GOULD, 2018). Zhang et al. conducted a study using a CRS rat model and found that ketamine can rapidly exert antidepressant effects by inhibiting the ferroptosis signaling pathway within nuclear complexes. Transmission electron microscopy revealed that CRS rats exhibited increased expression of TfR1 and decreased expression of FTH1 and GPX4, leading to ferroptosis, mitochondrial contraction, and chromatin condensation. Treatment with ketamine reversed these pathological reactions, leading to an improvement in depressive-like behavior in CRS rats (Zhang et al., 2022).

Electroconvulsive therapy (ECT) is an effective method for treating severe depression (REN et al., 2014). This procedure involves intravenous anesthesia, neuromuscular block, and mechanical ventilation. Commonly used intravenous anesthesia agents include propofol and etomidate, with etomidate having been shown to be more effective than propofol in terms of ECT efficacy (GUREL et al., 2022). Li et al. demonstrated, using a CUMS rat model, that etomidate used in ECT can protect hippocampal neurons from ferroptosis by modulating the BDNF/Nrf2 pathway, thereby enhancing the antidepressant effect of ECT. Nrf2 is an important player in the ferroptosis signaling pathway. The use of etomidate upregulates the expression of BDNF, Nrf2 and GPX4, thereby inhibiting ferroptosis in hippocampal neurons and improving depression-like states in rats. To further investigate the role of ferroptosis in ECT, the researchers administered ferrostatin-1 (Fer-1), as the most potential ferroptosis inhibitor (LONG et al., 2023), to the rats. Western blot analysis indicated significant upregulation of SLC7A11 and GPX4 in the CUMS model rats injected with Fer-1, while the levels of free Fe^{2+} decreased. Moreover, the combination of etomidate in ECT and Fer-1 exhibited a stronger antidepressant effect compared to etomidate in ECT alone (Li et al., 2023). Moreover, Li et al. discovered that Fer-1 reversed the upregulation of tsRNA-3029b induced by CUMS in mice. tsRNA-3029b knockdown suppressed ferroptosis and promotes cell regeneration of Corticosterone (CORT)-induced neuronal cells, leading to an improvement in depressive-like behavior in mice (LI E. et al., 2023). These findings demonstrate that both etomidate in ECT and Fer-1 reversed depressive behavior and hippocampal neuronal loss (Figure 3; Table 3).

In summary, abnormal ferroptosis signaling pathways leading to reduced neurotransmitter synthesis, lipid peroxide accumulation, mitochondrial dysfunction, and increased release of pro-inflammatory factors are important factors contributing to decreased neural plasticity, delayed synaptic growth and development, impaired neural network conduction, and neurotoxicity, ultimately leading to depression. The aforementioned studies provide compelling evidence for the critical role of ferroptosis in the pathogenesis and treatment of depression.

6 Conclusion and outlook

Depression is a prevalent mental disorder characterized by persistent symptoms such as low mood and reduced interest, with severe cases sometimes leading to suicidal tendencies, and has been a major contributor to poor global health and disability, with a recently increasing incidence (ZHANG X. et al., 2022; SHAHBAZI et al., 2022; SU and SI, 2022; YAO et al., 2022). Despite the continuous development of antidepressants, the treatment options for depression remain limited, often failing to provide sufficient relief for patients (WANG L. et al., 2023). Therefore, there is an urgent need to explore new strategies for developing antidepressant drugs (LEVENBERG and CORDNER, 2022). Recent research progress on the mechanism of ferroptosis suggests a close association between ferroptosis dysregulation and the pathological mechanism of depression (MAES et al., 1995b; WANG et al., 2019; LIANG et al., 2020; BERTHOU et al., 2021; WANG L. et al., 2023). This paper explored the efficacy of TCM ingredients, compound formulas, and antidepressant chemicals in regulating ferroptosis to combat depression, based on a thorough review of relevant literature reports.

While active ingredients and compound prescriptions of TCM hold significant research value, several challenges need to be addressed. The current focus on regulating the ferroptosis signaling pathway for depression treatment is primarily limited to animal models, lacking clinical research to validate its efficacy in patients. Many active ingredients in TCM present issues like poor stability, solubility, and difficulty crossing the BBB, which restrict their use in treating depression effectively. Furthermore, existing experimental research primarily targets single pathways or signals, neglecting the interactions between different targets or pathways. Additionally, validation methods such as gene knockout and antagonists are lacking, warranting further evidence to support the specificity of TCM and its targets. While antidepressant chemicals have shown positive effects in preclinical studies, their clinical application is limited due to side effects such as hallucinations, hepatotoxicity, neurotoxicity, and addiction. Similarly, ECT may result in adverse reactions like cardiac complications, cognitive impairment, and apnea, significantly limiting its use in clinical settings.

In future research, it is crucial to collect additional preclinical and clinical evidence, specifically focusing on the unique advantages of TCM in treating depression. It is necessary to conduct multicenter, high-quality, double-blind randomized controlled trials to further explore whether TCM formulas and their active ingredients can effectively regulate the ferroptosis signaling pathway, thereby improving depressive symptoms. Additionally, there is a need to enhance research on targeted delivery systems for active ingredients to increase drug concentration in the CNS and improve treatment efficacy (GERAILI et al., 2021). Integration of multiple omics techniques should be employed to explore additional ferroptosis signaling pathways and targets for depression treatment and prevention. It is also important to utilize reverse validation methods such as blockers or gene knockouts to further elucidate the mechanisms involved in the targeted regulation of ferroptosis by TCM formulas and active ingredients. Considerable work remains

in exploring the regulatory mechanisms of antidepressant therapies on ferroptosis, both in clinical and preclinical studies. These efforts are of great significance for the advancement of antidepressant research and development.

Author contributions

GZ: Writing–original draft, Writing–review and editing. SL: Writing–original draft. XZ: Writing–original draft. XL: Writing–review and editing. YY: Writing–review and editing. YL: Writing–review and editing. WY: Writing–review and editing. JL: Writing–review and editing. JT: Writing–original draft, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Katarzyna Stachowicz,
Polish Academy of Sciences, Poland

REVIEWED BY
Joanna Rzemieniec,
University of Milan, Italy
Bente Finsen,
University of Southern Denmark, Denmark
Jan Bert Gramsbergen,
University of Southern Denmark, Denmark

*CORRESPONDENCE
Shing-Chuan Shen,
scshen@tmu.edu.tw

†These authors have contributed equally to this work

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Antidepressant sertraline increases thioflavin-S and Congo red deposition in APPswe/PSEN1dE9 transgenic mice

Ming-Hsuan Liao[1], Yen-Kuang Lin[2], Fong-Ying Gau[3], Chun-Che Tseng[1], Da-Chih Wu[1], Chu-Yuan Hsu[4], Kuo-Hsuan Chung[5,6], Rung-Chi Li[7], Chaur-Jong Hu[8,9], Chee Kin Then[10,11†] and Shing-Chuan Shen[1,12,13*†]

[1]Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taipei, Taiwan, [2]Graduate Institute of Athletics and Coaching Science, National Taiwan Sport University, Taoyuan, Taiwan, [3]School of Nursing, College of Nursing, Taipei Medical University, Taipei, Taiwan, [4]School of Pharmacy, College of Pharmacy, Taipei Medical University, Taipei, Taiwan, [5]Department of Psychiatry and Psychiatric Research Center, Taipei Medical University Hospital, Taipei, Taiwan, [6]Department of Psychiatry, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, [7]Division of Allergy and Immunology, University of Virginia, Charlottesville, VA, United States, [8]Department of Neurology, Shuang Ho Hospital, College of Medicine, Taipei Medical University, Taipei, Taiwan, [9]Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, [10]MRC Oxford Institute for Radiation Oncology, Department of Oncology, University of Oxford, Oxford, United Kingdom, [11]Department of Radiation Oncology, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan, [12]International Master/Ph.D. Program in Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, [13]Department of Dermatology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

Introduction: Depression is strongly associated with Alzheimer's disease (AD). Antidepressants are commonly used in patients before and after their diagnosis of AD. To date, the relationship between antidepressants and AD remains unclear.

Methods: In our study, we administered sertraline or paroxetine to wild type (WT) and APPswe/PSEN1dE9 (APP/PSEN1) transgenic mouse models for up to 12 months. We quantified the drug concentrations using LC-MS/MS analysis and measured serum serotonin level using an ELISA assay. Additionally, we evaluated the amyloid burdens through thioflavin-S and Congo red stainings, and recognition memory using the novel object recognition test.

Results: Our findings revealed that mice treated with paroxetine exhibited a significantly higher level of weight gain compared to the control group and increased mortality in APP/PSEN1 mice. After 12 months of antidepressant treatment, the sertraline level was measured at 289.8 ng/g for cerebellum, while the paroxetine level was 792.9 ng/g for cerebellum. Sertraline significantly increased thioflavin-S and Congo red depositions, along with gliosis, in both isocortex and hippocampus of APP/PSEN1 mice compared to the control group. Both antidepressants also led to a decreased recognition index in APP/PSEN1 mice.

Conclusion: These findings suggest a potential role of sertraline in AD pathogenesis, emphasizing the need to reassess the use of these antidepressants in patients with AD.

KEYWORDS

sertraline, paroxetine, SSRI, β-amyloid, Alzheimer's disease, APP/PSEN1

Introduction

Alzheimer's disease (AD) is the most common cause of dementia, and is characterized clinically by a progressive and gradual decline of cognitive function. It is highly prevalent, incurable (Prince et al., 2013) and leads to huge social and economic burden around the world (Wimo et al., 2013). AD is characterized by reduced cholinergic transmission and neuronal death. Currently there is no cure for AD and the available treament, acetylcholinesterase inhibitors only provide some symptomatic relief (Mangialasche et al., 2010). The misfolded and aggregated proteins, β-amyloid (Aβ) peptide and hyperphosphorylated tau, have been postulated to be the cause of AD (Bloom, 2014). They have been used as biomarkers for diagnostic purposes (Braak and Braak, 1991; Thal et al., 2002) and therapeutic targets (van Dyck, 2018).

Depression is a common symptom which happen before or after the onset of AD and profoundly reduces the quality of life of AD patients. There are several possible hypotheses linking these two clinical entities: 1) Depression predisposes to AD, 2) depression presents as a symptom of AD, and 3) they are comorbidities which share similar pathogenesis (Saczynski et al., 2010; Byers and Yaffe, 2011; Li et al., 2011). As first-line treatment options for depression, the safety of antidepressants should be assessed in AD. The prevalence of antidepressant use has gradually increased around the world, especially the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRI), including in United Kingdom (Mars et al., 2017), United States (Pratt et al., 2017), the Netherlands (Noordam et al., 2015) and Taiwan (Wu et al., 2012).

Mounting evidence suggests that antidepressant medication is associated with an increased risk of dementia (Wang et al., 2018; Chan et al., 2019). In the Taiwanese database with a million datasets, our study showed that antidepressants may increase the risk of dementia, independent of the presence of depression (Then et al., 2017a). Consistent with this result, Heath et al. showed that paroxetine is associated with higher risk of dementia in elderly population (Heath et al., 2018). Our *in vitro* study also revealed that sertraline and paroxetine, two SSRIs, induced astrocyte apoptosis by triggering calcium overload (Then et al., 2017b). Sertraline was seen to possibly alter brain structures, including the hippocampus and anterior cingulated, in depressed or non-depressed monkeys (Willard et al., 2015). Morever, sertraline is toxic and causes behavioral alterations in planarian which serves as an alternative model for the study of neurotoxicity (Hagstrom et al., 2015; Thume and Frizzo, 2017). However, several experimental studies using transgenic AD mouse model (Nelson et al., 2007) or investigating human participants (Cirrito et al., 2011) have been published, showing the potential of antidepressants in ameliorating β-amyloid pathology, while some indicate no significant effect (Severino et al., 2018).

Neuroinflammation, characterized by astrocytosis and microgliosis, is driven by amyloid pathology and also exacerbates the pathogenesis of AD (Selkoe, 2001; Hensley, 2010). Misfolded and aggregated proteins evoke an innate immune response via binding to pattern recognition receptors of micro- and astroglia, which is associated with disease progression (Heneka et al., 2015). Forst et al. also proposed that reactive astrocytes surround Aβ plaques and contribute to the overall amyloid burden in the brain (Frost and Li, 2017). These studies highlighted that glial cells amplify neuronal damage via enhancement of neuroinflammation. Therefore, controlling the proinflammatory process could be a therapeutic approach in AD (Bronzuoli et al., 2016).

Human population studies and *in vitro* studies showed that antidepressants, including sertraline and paroxetine, are associated with the risk of dementia or AD. The high prevalance of antidepressant medications in the world, coupled with a limited investigation of the consequences of chronic treatment with SSRIs, especially sertraline and paroxetine, highlights the importance to re-assess their safety in terms of AD. Therefore, we conducted an *in vivo* study for up to 12 months to investigate the impact of sertraline and paroxetine on thioflavin-S and Congo red deposition in AD transgenic (APP/PSEN1) mouse model.

Materials and methods

Animals

We obtained approval from the Taipei Medical University Institutional Animal Care and Use Committee. We used B6C3 hybrid background (C57BL/6 X C3H/HeN), double transgenic (Tg) APPswe/PSEN1dE9 (APP/PSEN1) mice (Jankowsky et al., 2001), and littermate wild type (WT) mice which were purchased from National Applied Research Laboratory, Taiwan (N = 66, n = 12 for each wild type group and n = 11 for each AD group). Mice were genotyped in-house with primers for APP (transgene F-AGGACTGACCACTCGACCAG, R-CGGGGGTCTAGTTCTGCAT; internal positive control F-CAAATGTTGCTTGTCTGGTG, R-GTCAGTCGAGTGCACAGTTT) and PSEN1 (transgene F-AATAAGAACGGCAGGAGCA, R-gCCATGAGGGCACTAATCAT; internal positive control F-CTAGGCCACAGAATTGAAAGATCT, R-GTAGGTGGAAATTCTAGCATCATCC). Only male mice were used in this study to avoid the confounding factor of mouse estrous cycle. All mice, regardless of their WT or APP/PSEN1 status and antidepressant treatment, were randomly allocated to cages. Between two and five mice were housed in each cage, depending on the supply conditions. Animals were fed with food and water *ad libitum* in 12 h light/dark cycle with constant temperature and humidity. We inspected the mice daily and recorded body weight weekly to assess their health. During euthanisation, an overdose of anaesthetic agents was used at study termination.

Treatments of sertraline and paroxetine

Sertraline (CenZoft concentrate solution 20 mg/mL, Center) or paroxetine (Seroxat 15 mg, GSK) was administered in drinking water initially at a dose of 25 mg/kg/day and 10 mg/kg/day respectively. Treatment was initiated at 3 months of age, and was continued for a duration of 12 months. However, we observed unexpected sudden mortalities in APP/PSEN1 transgenic mice treated with initial dose of paroxetine (10 mg/kg/day), and no significant abnormal gross finding was confirmed by veterinarian. Therefore, we decreased the dosage to 5 mg/kg/day four and a half months following the initial treatment.

Quantification of sertraline and paroxetine concentrations in serum and brain

To identify the sertraline and paroxetine concentrations in serum and brain, LC-MS/MS analysis, by using the mass spectrometer (Agilent triple quadrupole 6470), was performed on mouse samples after 12 months treatment of antidepressants based on the previous modified methods (Peng et al., 2008; Olesen et al., 2016). During sacrification, blood samples were collected by cardiac puncture and centrifuged for 10 min at 1,500 × rpm. The supernatant was stored at −80°C freezer for further analysis. 50 µL of serum was added with 5 µL of internal control (fluoxetine; concentration: 1,000 ng/mL), 50 µL sodium hydroxide (concentration: 0.1 M) and 0.5 mL ethyl acetate. The mixture was vortexed thoroughly for 2 min. The supernatant of the organic phase was collected and centrifuged at 13,000 × *g* for 5 min. For cerebellums, they were stored at −80°C after perfusion fixation by formaldehyde solution. Mouse cerebellums were added with 600 µL ethyl acetate and 5 µL of internal control (fluoxetine; concentration: 1,000 ng/mL), then homogenized by tissue homogeniser (Kurabo Sh-100) for 90 s at 1,600 × rpm, and then centrifuged at 2,500 × rpm for 10 min at 4°C. A volume of 300 µL top organic layer was further transferred to eppendorf tubes and centrifuged at 13,000 × rpm for 5 min. Both supernatant from processing of plasma and cerebellum was filtered by PVDF (0.22 µm) followed by LC-MS/MS analysis. Two MRM transitions were monitored for sertraline, paroxetine and fluoxetine (sertraline: 306.3–275.2; paroxetine: 330.1–192.2; fluoxetine: 310.1–148.1; Supplementary Figure S1). Calibration was performed by linear calibration based on nine-points and the range was 1–640 ng/mL.

Quantification of serotonin and brain-derived neurotrophic factor (BDNF)

The serum samples were prepared as the same procedure described in the previous section for the quantification of sertraline and paroxetine. The serotonin and BDNF levels in the serum was quantified using the ELISA kits for ST/5-HT (5-hydroxytryptamine; FineTest EU0253) and for BDNF (Cloud clone SEA011Mu). Firstly, the plates were washed, and then 50 µL of standards, samples, or blanks were added to the pre-coated plate, along with 50 µL of biotin-labeled antibody. The plate was sealed, gently tapped, and incubated at 37°C for 45 min. Subsequently, a washing step was carried out, followed by the addition of 100 µL of HRP-Streptavidin Conjugate. After another washing step, 90 µL of 3,3′,5,5′-Tetramethylbenzidine (TMB) substrate was added, followed by 50 µL of Stop Solution. The absorbance of the plates at 450 nm was measured using the Bio-Tek µQuant Universal Microplate Spectrophotometer.

Tissue preparation

The mice were sacrificed under a general anaesthesia overdose, followed by transcardial perfusion with ice-cold PBS and 10% formaldehyde. Subsequently, the brains were collected and kept in 10% formaldehyde for 24 h, followed by preservation in 70% ethanol at 4°C. The tissues were trimmed, and dehydrated with serial alcohol solution. They were then embedded in paraffin wax, and were cut to a thickness of 3 µm. Coronal brain tissue sections, intended for histopathological assessment, were obtained with the specific aim of capturing cuts that encompassed a sufficiently large area of the hippocampus. These sections were positioned approximately 2.3 mm caudal to the bregma, in accordance with the mouse brain atlas by Paxinos and Franklin (Paxinos and Franklin, 2001). This location corresponded to approximately 8.3 mm from the cranial apex.

Hematoxylin and eosin (H&E)

For H&E staining, the paraffin section slides underwent deparaffinization with xylene and hydration using serial alcohol solutions. The sections were stained with hematoxylin solution (BioTnA TA01NB) for 1 min, followed by a 5-min wash with running tap water. Subsequently, the slides were counterstained with Eosin (BioTnA TA01ES) for 1 min. Dehydration with alcohol, clearance in xylene, and mounting with mounting medium followed.

Brain lesions in H&E-stained sections were assessed and graded by a veterinary histopathologist based on the INHAND (International Harmonization of Nomenclature and Diagnostic Criteria) (Shackelford et al., 2002). Evaluated areas and parameters included acidophilic material (characterized by strong eosinophilic deposits in the centre surrounded by pale-stained structures in a radial pattern), atrophy (decreased volume/cell counts), and gliosis (characterized by densely stained and small-sized elements) of the isocortex and hippocampus. Grading was performed as follows: Grade 0 - no remarkable histopathological changes (<1%); Grade 1 - minimal (1%–5%); Grade 2 - slight (5%–25%); Grade 3 - moderate (26%–50%); Grade 4 - moderately severe (51%–75%); Grade 5 - severe/high (>75%).

Thioflavin-S staining

For thioflavin-S staining, the slides were deparrafinized and hydrated with xylene and serial alcohol solutions. Stains were performed with 1% thioflavin-S solution (Sigma-Aldrich) for

10 min, and then the slides were washed in running tap water for at least 10 min. The slides were then dehydrated with alcohol, cleared in xylene, and mounted with mounting medium.

Thioflavin-S staining was quantified both automatically, involving the calculation of the positive staining area relative to the entire brain, and manually, by counting the number of positive spots in the cortex and hippocampus. These assessments were conducted in a blinded fashion. Additionally, we engaged a veterinarian pathologist in identifying true positive signals to perform these assessments in a blinded manner.

Congo red staining

Congo red staining was performed by using the stain kit (BIOTnA Biotech TASS12) to identify amyloids. After deparaffinization and hydration, the slides were stained by congo red solution for 15–20 min followed by rinsing in distilled water. They were then immersed in alkaline alcohol solution for differentiation and hematoxylin for counterstaining. Following dehydration, the slides were cleared in xylene and mounted with resinous mounting medium. We captured the images by using a compound optical microscope (Olympus, Japan) and analyzed the Congo red staining spots using ImageJ.

Immunofluorescence and immunohistochemistry stainings

For immunofluorescent staining of anti-glial fibrillary protein (GFAP), following deparaffinization and hydration, the slides were blocked with 10% BSA in PBS and incubated with the primary antibody against GFAP (1:600; Genetex GTX108711) at 4°C overnight. Subsequently, the slides were incubated with the secondary antibody Alexa Fluor 488 (1:750; Abcam ab150077) for 1 hour at room temperature. Both primary and secondary antibodies were diluted in 3% BSA in PBS. The slides were mounted with a fluorescence mounting medium containing DAPI (Origene). Immunofluorescence was visualized and captured using a confocal microscope (Stellaris 8 confocal microscope, Leica).

For immunohistochemistry staining, the primary antibodies and their dilutions were anti-phospho-mixed lineage kinase domain-like protein Ser345 (pMLKL; 1:200; NovusBio NBP2-66953) and anti-ionised calcium-binding adapter molecule 1 (IBA1; 1:200; Bioworld BS90680). The slides were scanned using a MoticEasyScan Pro 6 at ×40 magnification.

For both staining techniques, positive-stained cells and total cell counts were manually calculated at ×40 magnification.

Behavioural tests

To assess the long-term memory, mice were subjected to the novel object recognition test (NORT) based on modified methods from a previous study (Zhang et al., 2012). The novel object recognition tests were conducted at 3 and 12 months post antidepressants in a rectangular white arena (60 cm × 80 cm, surrounded by 60 cm-high walls). The entire assessment consisted of 4 phases: pre-habituation, habituation, training, and testing. On the first day, animals were brought to the testing room to freely explore the box in the absence of objects for 5 min. On the second and third day, mice were habituated to the empty box for 20 min per day. On the fourth day, each mouse took a training trial with exploration of two identical objects for 10 min and followed by a testing trial after an inter-session interval of 1 h. During the testing, animals were placed back to the same box, where one of the two familiar objects was switched to a novel one, to start a 5 min testing phase. Recording videos were analyzed by using ACTUAL TRACK software. Object exploration time was defined as the length of time the subject spent sniffing, pawing, or directed its nose within 2 cm of the object. Sitting or standing on the object was not recognized as exploration. The exploration time was analyzed manually using 2 stop watches. In the training session, the location preference in the training phase and recognition index (RI) in the testing phase were calculated using the following formula:

Recognition index (RI) = Time exploring novel object/(Time exploring novel object + Time exploring familiar object)×100%

The contextual fear conditioning was done at 15 months of age to evaluate by measurement of the tendency of freezing behavior. On training day, mice were given 3 min of exploration in a chamber with current-regulated shocker (Coulbourn Instruments) and followed by 2 s of electric footshock (0.75 Ma). Mice were then removed from the chamber 30 s later. The testing was performed 24 h following the training day, mice were returned to the chamber and freezing behaviour was recorded for 3 min. Freezing was defined as the absence of any movement with treshold of more than 1 s. Freezing was measured using the FreezeScan video tracking system and software (CleverSys).

The behavioral tests were carried out in a blinded manner, with the individuals conducting the tests unaware of the group assignments.

Statistics

All of the data are presented as mean ± SD. All statistic analyses were performed using GraphPad Prism (GraphPad Software, Inc., San Diego, CA). The Log-rank test was used for survival analysis, and one-way ANOVA followed by Dunnett's multiple comparisons test was employed for other comparisons. Significance was set at 0.05.

Results

Paroxetine increased body weight in both WT and APP/PSEN1 transgenic mice, while reduced survival in APP/PSEN1 mice

Both WT and APP/PSEN1 mouse model were used to study the effect of antidepressants on initiation and progression of AD. Sertraline and paroxetine were administered in drinking water for a period of 12 months to study the long term effects of these medications. The daily dose of sertraline was 25 mg/kg/day, while paroxetine was initially given at a dosage of 10 mg/kg/day for the first four and a half months, and then reduced to 5 mg/kg/day for the remainder of the study. These initial dosages were chosen based on

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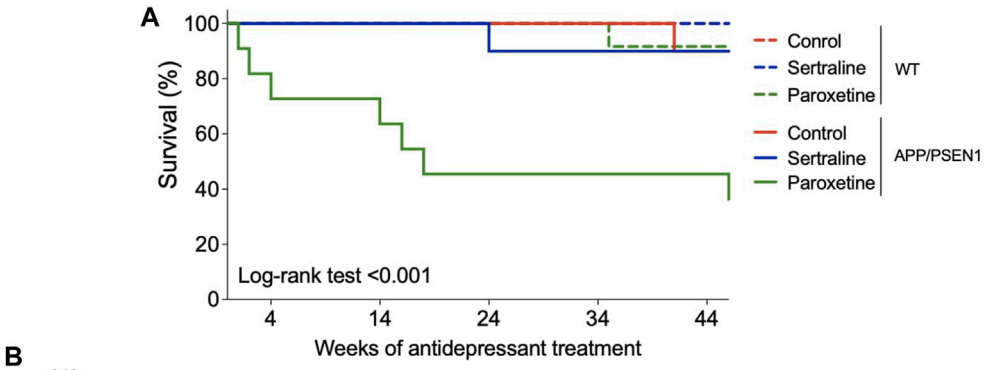

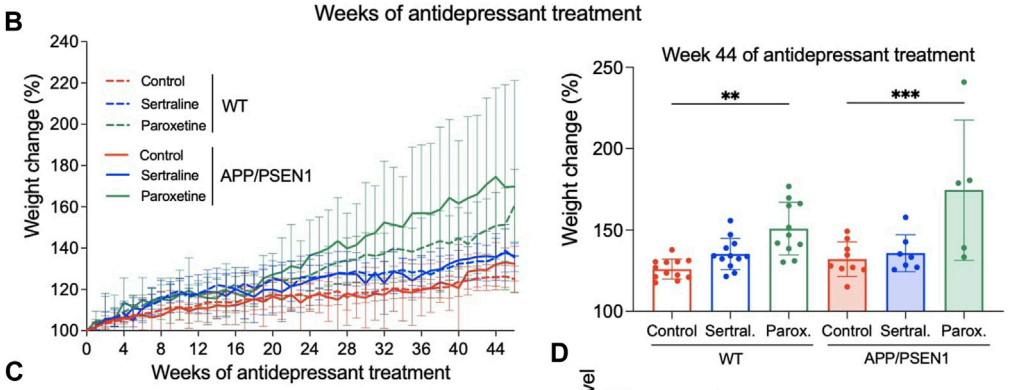

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		Serum (nmol/L)			Cerebellum (ng/g)		
		Mean	SD	n	Mean	SD	n
Sertraline	WT	9.8	8.7	10	400.1	374.6	11
	APP/PSEN1	6.9	6.1	7	154.9	208.0	9
	Mean	**8.6**	**7.7**	**17**	**289.8**	**328.2**	**20**
Paroxetine	WT	139.6	97.5	10	918.3	512.2	11
	APP/PSEN1	54.8	34.5	3	333.3	70.7	3
	Mean	**120.0**	**93.4**	**13**	**792.9**	**514.4**	**14**

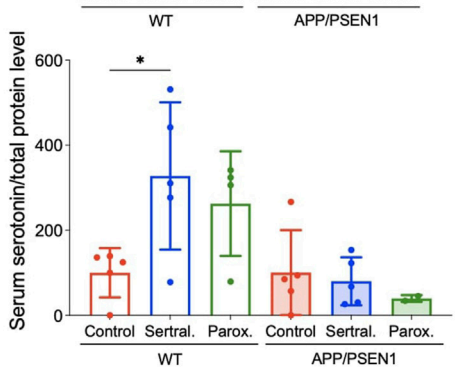

FIGURE 1
Sertraline and paroxetine increased body weight and accumulated to the level of hundreds ng/g in mouse cerebellum. **(A)** Kaplan-Meier (KM) plots of survival percentage among WT and APP/PSEN1 mice with different treatments. **(B)** Growth curve of mice in different groups (N = 60). Comparison of weight among different groups in WT and AD mice at week 44 after starting treatment treatment. **(C)** Sertraline and paroxetine levels in serum (nmol/L) and cerebellum (ng/g) tissues of WT and APP/PSEN1 mice fed with antidepressants for 12 months by using LC-MS/MS. **(D)** Serum serotonin levels of WT and APP/PSEN1 mice post antidepressant. Data are means ± SD. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

the recommendations provided in the guide for treating neuropsychiatric symptoms of AD patients (Lleo et al., 2006) and the dosages employed in animal models (Taler et al., 2013). Unexpected sudden mortalities happened in paroxetine group, which was limited to APP/PSEN1 mice ($p < 0.001$; Figure 1A). For both WT ($p = 0.004$) and AD ($p < 0.001$) mice, the groups treated with paroxetine demonstrated more weight gain compared to control groups (Figure 1B).

High levels of sertraline and paroxetine were detected in cerebellums

To determine the antidepressant levels in systemic circulation and central nervous system, we performed LC-MS/MS analysis by using serum and cerebellum tissues. Data confirmed the existence of sertraline in our samples with acquisition time of 7.964 min and MRM transition of 306.3 to 275.2 (Supplementary Figure S1A), and acquisition time of 7.609 min and MRM transition of 330.0 to 192.0 for paroxetine (Supplementary Figure S1B). After pooling data from WT and APP/PSEN1 mice, sertraline was shown to be 8.6 nmol/L (n = 17) in serum and 289.8 ng/g (n = 20) in cerebellum, while paroxetine was 120.0 nmol/L (n = 13) in serum and 792.9 ng/g (n = 14) in cerebellum (Figure 1C). These results were in consistent with the serum concentrations of antidepressants from patients' samples (Reis et al., 2009).

Sertraline and paroxetine belong to the class of SSRIs, which elevate extracellular serotonin levels by inhibiting its reabsorption by presynaptic cells. To determine whether the SSRI concentration was sufficient to impact the physiology of mice in this model, we quantified serum serotonin levels to assess the impact of the SSRI concentration on mouse physiology in this model. We observed a significant increase in serum serotonin levels in WT mice treated

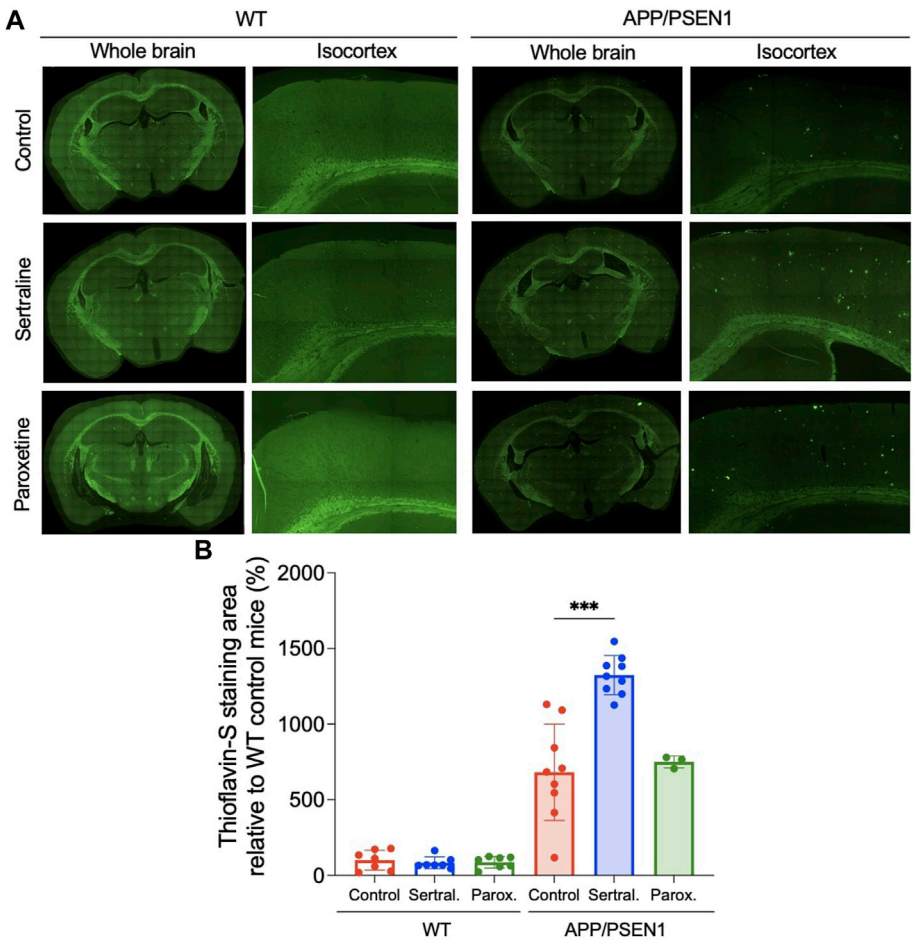

FIGURE 2
Sertraline increased thioflavin-S deposits in APP/PSEN1 mice. **(A)** Representative images of thioflavin-S staining in both WT and APP/PSEN1 mice. **(B)** Comparison of thioflavin-S deposition in WT and APP/PSEN1 transgenic mice after receiving only water (n = 9), sertraline (n = 9) and paroxetine (n = 3) for up to 12 months. Data are means ± SD. Comparison was done by ordinary one-way ANOVA followed by Dunnett's multiple comparison test. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

with sertraline ($p = 0.01$; Figure 1D), and a non-significant trend towards elevated serum serotonin levels in the paroxetine group. However, these effects were not observed in the APP/PSEN1 mice. As for BDNF, a protein crucial for stimulating the growth and preservation of neurons, no significant changes were observed among all groups (see Supplementary Figure S2).

Sertraline significantly increased thioflavin-S and Congo red deposits in APP/PSEN1 mice

By using thioflavin-S staining to evaluate the β-amyloid deposition, we observed minimal thioflavin-S deposit in WT mice across all treatment groups (Figure 2A left panel and Figure 2B). However, sertraline ($p < 0.001$) significantly increased the total area of thioflavin-S deposit compared to control group in APP/PSEN1 mice, as quantified automatically using ImageJ software (Figure 2A right panel and Figure 2B). This finding aligns with the result measured by a veterinary pathologist ($p = 0.001$; Supplementary Figure S3A). To further investigate the brain areas affected, we manually counted the thioflavin-S deposits in a blinded manner and observed a significantly higher number of deposits scattered across the isocortex ($p < 0.001$) and hippocampus ($p < 0.001$; Supplementary Figure S3B). These findings were supported by Congo red staining, which revealed that sertraline increased deposits in both the isocortex ($p = 0.003$) and hippocampus ($p < 0.001$) of APP/PSEN1 mice (Figure 3). We also found that paroxetine exacerbated the deposition in the hippocampus of APP/PSEN1 mice ($p = 0.004$).

Sertraline induced elevated acidophilic material and gliosis in the isocortex and hippocampus of APP/PSEN1 mice

In the APP/PSEN1 mice, elevated levels of acidophilic material and gliosis were observed in both the isocortex ($p = 0.020$ and $= 0.004$) and hippocampus ($p < 0.001$ and $= 0.004$) of the sertraline-treated group when compared to the control group (Figures 4A, B). It is noteworthy that the acidophilic materials were surrounded by glial cells (Supplementary Figure S4). Additionally, there was a non-

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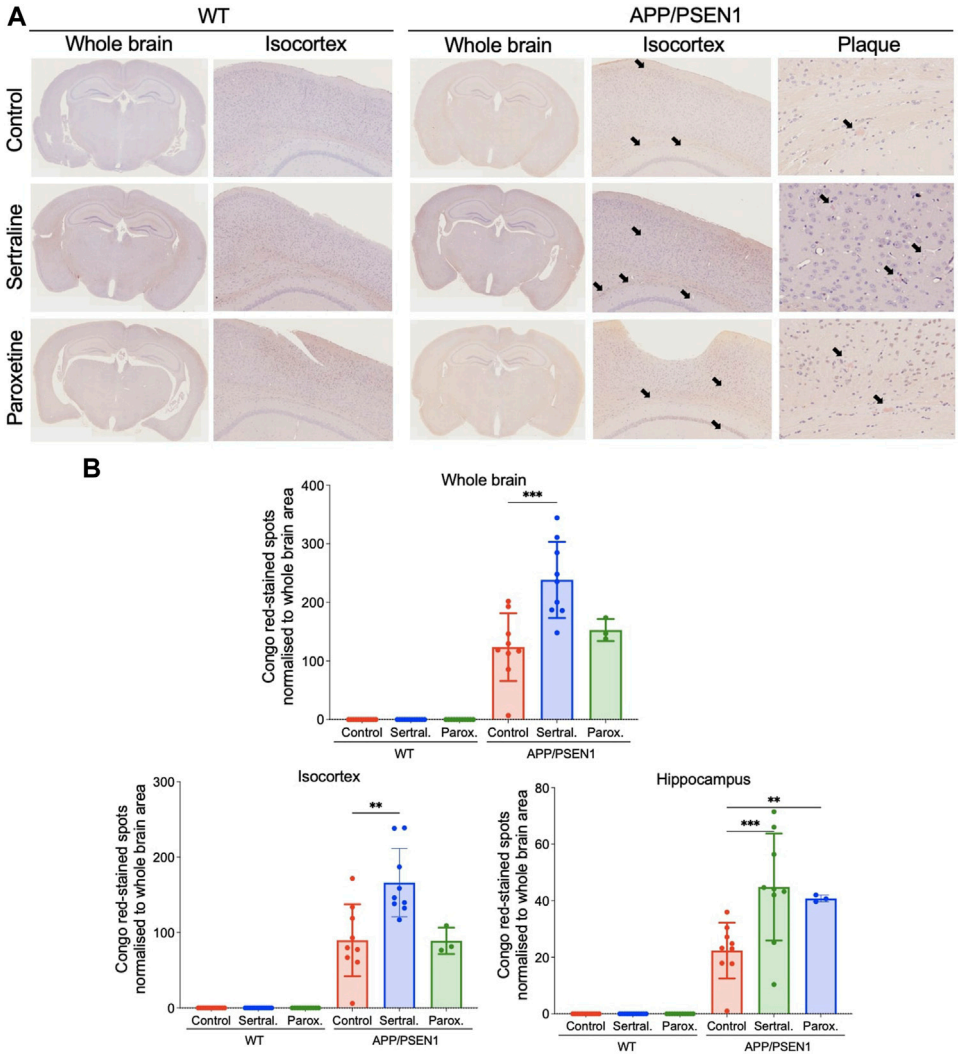

FIGURE 3
Sertraline increased Congo red-stained spots in APP/PSEN1 mice. **(A)** Representative images of congo red-stained spots in both WT and APP/PSEN1 mice (black arrows) and **(B)** the spot counts in the whole brain, isocortex and hippocampus. Data are means ± SD. Comparison was done by ordinary one-way ANOVA followed by Dunnett's multiple comparison test. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

significant trend indicating an increased presence of Iba-1$^+$ cells, a microglial marker, in the sertraline-treated APP/PSEN1 mice (Supplementary Figure S5). In contrast, paroxetine significantly exacerbated the gliosis ($p = 0.020$) and also led to hippocampal atrophy ($p = 0.010$) in the APP/PSEN1 mice (Figure 4A, middle and right panels). This treatment was also associated with a trend of increased GFAP$^+$ cells, an astrocyte marker, in both WT and APP/PSEN1 mice (Supplementary Figure S5).

A trend of decline of short-term memory in sertraline and paroxetine groups of APP/PSEN1 mice at 12 months post antidepressants

Novel object recognition test was performed to evaluate the cognitive function of mice with or without antidepressants (Figure 5A). The results showed sertraline ($p = 0.009$) and paroxetine ($p = 0.04$) significantly reduced recognition memory of WT mice 3 months after antidepressants administration (Figure 5B left), while the cognition of APP/PSEN1 mice in sertraline ($p = 0.03$) and paroxetine ($p < 0.001$) group were decreased in 12 months (Figure 5B right). However, no significant difference among groups was found in the contextual fear conditioning (Supplementary Figure S6). The result implied that sertraline and paroxetine impair memory function after long-term antidepressant medication.

Discussion

This is the first study to demonstrate that sertraline and paroxetine enhanced the thioflavin-S deposition in APP/PSEN1 mice, indicating these two SSRIs might accelerate the pathogenesis of AD. Thioflavin-S deposit was not detected in

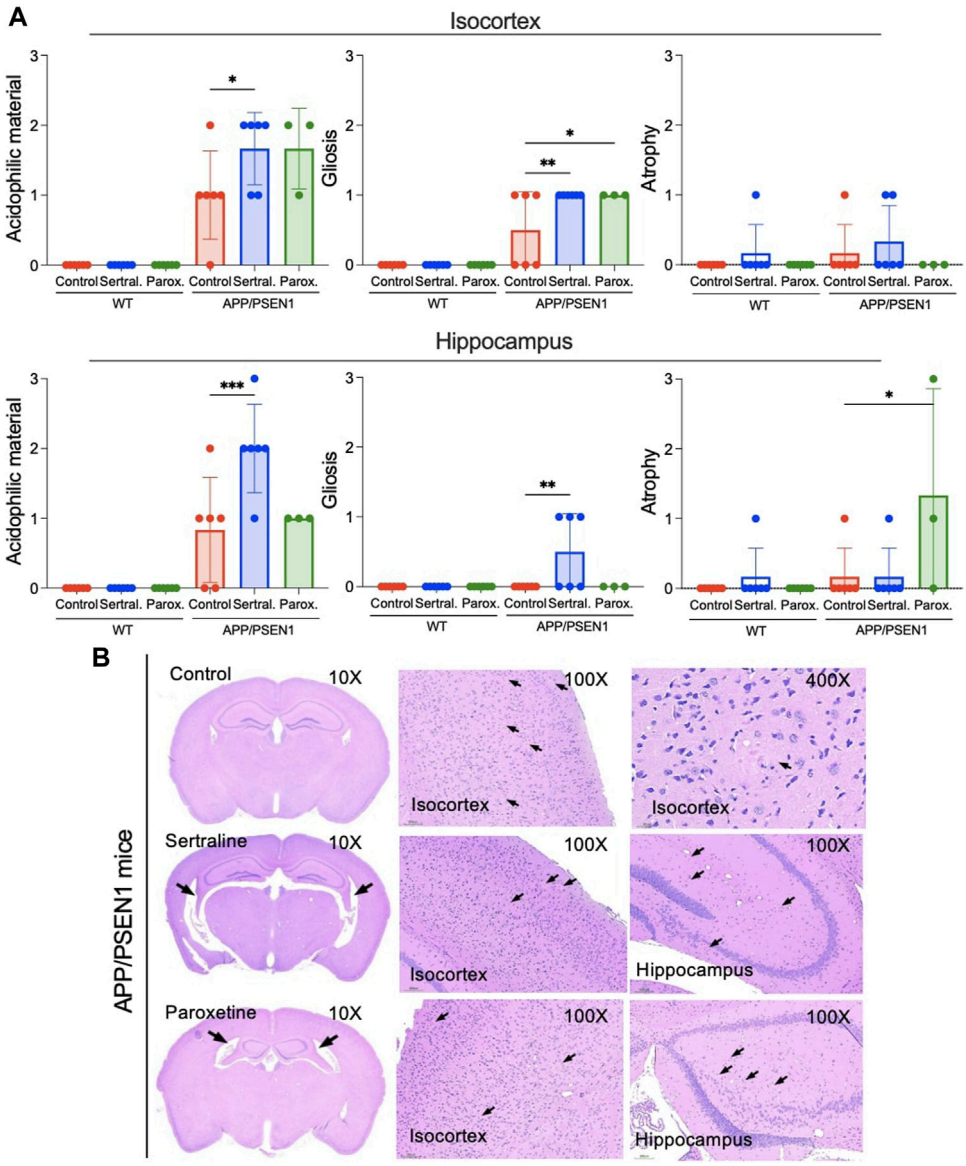

FIGURE 4
Sertraline induced an increase in the acidophilic material and gliosis in the isocortex and hippocampus in APP/PSEN1 mice. **(A)** Statistical analysis of severity of the acidophilic material, gliosis and atrophy in the isocortex and hippocampus of APP/PSEN1 mice graded by veterinary histopathologist based on the INHAND. **(B)** APP/PSEN1 mice were observed with only a mild level of the acidophilic material in the control group. It was significantly higher in the sertraline group. Arrows indicate the brain lesions. Data are means ± SD. Comparison was done by ordinary one-way ANOVA followed by Dunnett's multiple comparison test. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

WT mice, regardless of control or antidepressant groups, which suggests that antidepressant alone is not sufficient to induce the formation of β-amyloid. The chronic toxicity of paroxetine was observed exclusively in APP/PSEN1 mice, emphasizing the importance of studying the potential side effects of this medication in AD patients.

In vitro studies have shown that sertraline and paroxetine, below 10 μM, promote neurogenesis and ameliorate inflammatory response (Anacker et al., 2011; Peng et al., 2013; Lu et al., 2019). In contrast, above 10 μM, sertraline and paroxetine are toxic to astrocytes and neurons (Then et al., 2017b). It is worth investigating the effects of the cumulative concentration of antidepressants on the central nervous system in mouse models and human studies because of these seemingly conflicting results. In order to study the concentration which is achievable in patient in clinical settings, we used the dosage prescribed for patients (Lleo et al., 2006) in this study. We performed high performance liquid chromatography to determine the concentration of sertraline and paroxetine in brain and serum. Our results aligns with the serum concentration of 131 nmol/L for paroxetine, as proposed by Reis et al., 2009. However, in contrast to their study, our findings indicated a lower level of paroxetine compared to the reported concentration of 67 nmol/L. In addition, Peng et al. showed that the brain/blood ratio of sertraline is more than 45 which showed a high level of antidepressant in the brain tissue compared to serum (Peng et al., 2008). We also found high levels of sertraline and paroxetine in brain tissue which suggests the increased thioflavin-S and

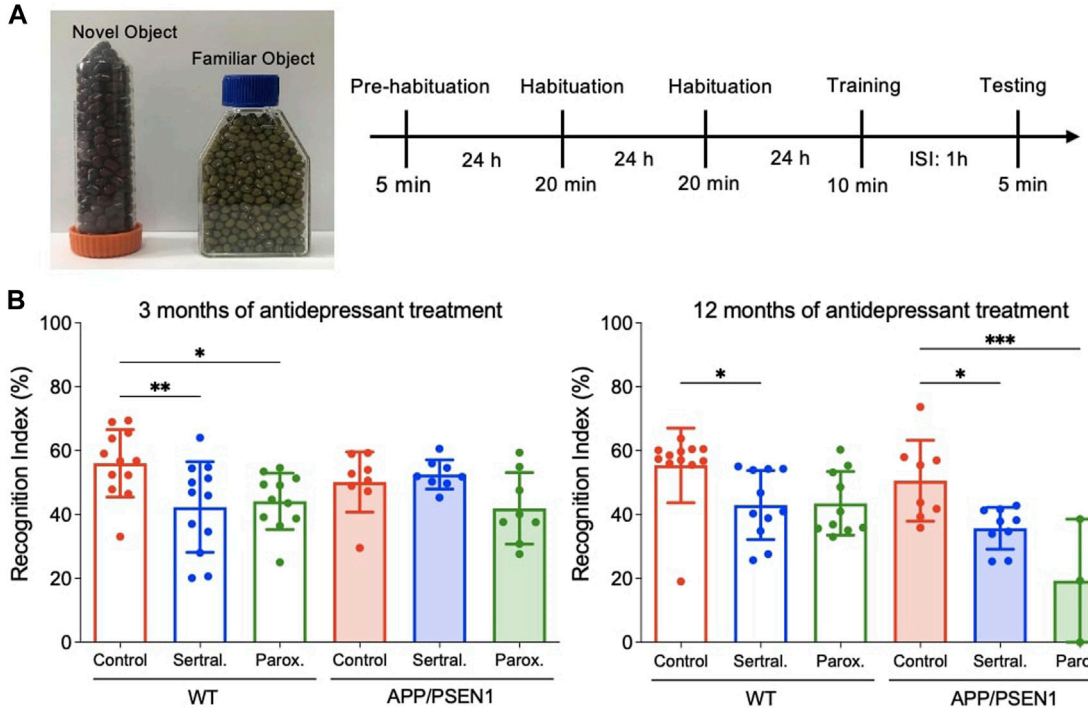

FIGURE 5
Sertraline and paroxetine worsened short-term memory in 15-month-old APP/PSEN1 mice. **(A)** Schematic diagram of novel object recognition test. **(B)** Recognition index of different groups at 6 month-old and 15-month old. Data are means ± SD. Comparison was done by ordinary one-way ANOVA followed by Dunnett's multiple comparison test. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

Congo red deposits could be the consequence of exposure to high level of antidepressant medication.

To assess the cognitive function of mice, we conducted novel object recognition tests at 3 months and 12 months post-antidepressant administration. At 3 months, impaired recognition memory was observed in the sertraline and paroxetine groups of WT mice. It is essential to note that control AD mice already exhibited a tendency towards a lower recognition index compared to control WT mice at this time point, and no significant differences in the recognition index were observed among all groups of APP/PSEN1 mice. At 12 months, in addition to the impaired recognition function observed in sertraline-treated WT mice and a non-significant trend in the paroxetine group, we also found a decline in the recognition index in the antidepressant groups of APP/PSEN1 mice. This suggests that memory was impaired by sertraline and paroxetine in aged AD mice, leading them to spend less time exploring a novel object. Sperling et al. suggested that the deterioration of clinical function may occur at a later stage, subsequent to the presence of elevated levels of β-amyloid and cognitive impairment (Sperling et al., 2011). We found that the weight of mice treated with sertraline and paroxetine were significantly higher than that of the control group. This result suggested that the antidepressants, given for a duration of 12 months, may decrease mouse metabolism. We also conducted a contextual fear conditioning test and found no significant differences among the groups. Although both behavior tests evaluate memory and learning capabilities, they differ in the type of memory they assess and the brain regions involved. The novel object recognition test focuses on non-associative memory and engages brain regions linked to the medial temporal lobe, including the hippocampus and perirhinal cortex (Kinnavane et al., 2016). In contrast, contextual fear conditioning examines associative, emotional, and fear-related memory and also relies on the hippocampus for context encoding (Kim and Cho, 2020). Furthermore, it is noteworthy that pathological changes consistently preceded observable behavioral changes (Sperling et al., 2011). In this model, β-amyloid deposits develop by 6 months, and cognitive deficits become detectable at 12 months (Janus et al., 2015). It is possible that the memory deficits observed may not be severe enough to manifest in both tests.

To further study the possible mechanism of sertraline-increased thioflavin-S and Congo red deposits, we further investigated other histological phenotypes in these mice. In APP/PSEN1 mice treated with sertraline, we observed mild gliosis in the isocortex and hippocampus, surrounding the acidophilic material. However, the causal relationship between thioflavin-S and Congo red deposition and gliosis remains elusive in this study, as gliosis could be either the cause or consequence of β-amyloid accumulation. Previous studies have shown controversial results of pro- and anti-inflammatory effects of sertraline and paroxetine (Maes et al., 1999; Marques-Deak et al., 2007; Tynan et al., 2012), while inflammation has been proposed as a central mechanism in exacerbating the pathogenesis of AD (Kinney et al., 2018). Notably, an *in vitro* study has demonstrated that both sertraline and paroxetine elevate BDNF levels and offer neuroprotection by enhancing the overall outgrowth of hippocampal dendrites under toxic conditions. (Seo et al., 2014). In addition, sertraline also reduced inflammatory processes in the rat hippocampus during the onset of seizures (Sitges et al., 2014). Moreover, sertraline and

paroxetine suppressed microglial responses to an inflammatory stimulus by reducing tumour necrosis factor-alpha (TNF-alpha) and nitric oxide (NO) production after stimulation with lipopolysaccharide (Tynan et al., 2012). A more in-depth investigation into the relationship between AD pathology and neuroinflammation, including the involved immune cells and biological processes, is warranted.

In this section, we review other studies and discuss the impact of chronic SSRI treatment on the formation of β-amyloid, considering potential outcomes such as protective effects, no discernible impact, or an increase in plaque load. Consistent with our results, Severino et al. and Sivasaravanaparan et al. showed that chronic paroxetine therapy, administered at a dosage of 10 mg/kg/day in drinking water, elevated mortality rates in APP/PSEN1 transgenic mice aged 9–18 months (Severino et al., 2018; Sivasaravanaparan et al., 2022). Notably, a substantial improvement in survival outcomes was observed when the dosage was reduced to 5 mg/kg/day during the same age range. It is worth noting that paroxetine did not exhibit a reduction in amyloid pathology in the neocortex and hippocampus of APP/PSEN1 transgenic mice, as assessed through immunohistochemistry staining of β-amyloid. Additionally, the administration of paroxetine led to an increase in body weight in WT mice. Our investigation on APP/PSEN1 mice demonstrated that paroxetine also increased mortality, as well as Congo red-stained deposition in the hippocampus. In a 3xTg AD mouse model, daily intraperitoneal injections of 5 mg/kg paroxetine over 5 months significantly decreased levels of amyloid β-peptide in hippocampal and neocortical tissues, as determined by ELISA assay (Nelson et al., 2007). Additionally, the number of β-amyloid immunoreactive neurons in the hippocampus reduced, as assessed using IHC. While Tin et al. showed a 70% inhibition of β-amyloid aggregation at 100 μM of paroxetine in the aggregation kinetic experiment, this finding has not been validated in cell or animal studies (Tin et al., 2018). Our *in vitro* study found that this concentration is five times higher than what could induce astrocyte apoptosis (Then et al., 2017b).

Amoxapin, a tricyclic antidepressant (TCA), at a concentration of 10 μM for 24 h, has been reported to reduce β-amyloid generation as assessed using ELISA analysis in a human neuroblastoma cell line (Li et al., 2017). This reduction involves multiple serotonin receptor 6 (HTR6)-mediated targets, including β-arrestin2 and CDK5 (Li et al., 2017). This aligns with evidence indicating that TCAs are relatively safe for astrocytes compared to sertraline and paroxetine (Then et al., 2017b). Furthermore, Sheline et al. demonstrated that intraperitoneal citalopram, found to be non-cytotoxic to astrocytes in our *in vitro* study, reduced Aβ levels in brain interstitial fluid (ISF) (Sheline et al., 2014). This effect, observed using *in vivo* microdialysis probes implanted in the hippocampus, occurred in a dose-dependent manner, with doses ranging from 5 to 20 mg/kg administered intraperitoneally within 1 day in aged APP/PSEN1 plaque-bearing mice. Additionally, Cirrito et al. showed that other SSRIs, namely, fluoxetine (10 mg/kg), desvenlafaxine (30 mg/kg), and citalopram (5 and 10 mg/kg) administered intraperitoneally, reduced brain interstitial fluid (ISF) Aβ levels within 24 h in a mouse model of AD, as measured by *in vivo* microdialysis. Morever, a history of taking antidepressants within the past 5 years was associated with fewer cortical amyloid plaques in human participants, as quantified by PET imaging (Cirrito et al., 2011). Despite evidence supporting short-term treatments of antidepressants from different classes, such as amoxapine (TCA) and citalopram (SSRI) in mitigating Aβ deposition, there is a lack of studies concerning chronic administration of sertraline and paroxetine. To our knowledge, this study is the first to show long-term usage of sertraline increases thioflavin-S and Congo red deposition in APP/PSEN1 mice, along with a decline in recognition function.

Conclusion

In this study, sertraline accumulated in brain tissues and significantly increased thioflavin-S and Congo red deposits in the isocortex and hippocampus of APP/PSEN1 mice. Additionally, these antidepressants were found to enhance gliosis and impair cognitive function. Further research is necessary to investigate the safety of antidepressant medication, specifically sertraline and paroxetine, when used by patients with AD.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

The animal studies were approved by the Taipei Medical University Institutional Animal Care and Use Committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the owners for the participation of their animals in this study.

Author contributions

M-HL: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Writing–original draft. Y-KL: Data curation, Formal Analysis, Investigation, Methodology, Software, Supervision, Writing–original draft, Writing–review and editing. F-YG: Conceptualization, Formal Analysis, Methodology, Project administration, Writing–original draft. C-CT: Conceptualization, Data curation, Formal Analysis, Investigation, Writing–original draft. D-CW: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing–original draft. C-YH: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Writing–original draft. K-HC: Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Validation, Writing–review and editing. R-CL: Formal Analysis, Funding acquisition, Project administration, Resources, Supervision, Writing–review and editing. C-JH: Funding acquisition, Project administration, Resources, Supervision, Validation, Writing–review and editing. CT: Formal Analysis, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing–review and editing. S-CS: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Visualization, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1260838/full#supplementary-material

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EDITED BY
Magdalena Sowa-Kucma,
University of Rzeszow, Poland

REVIEWED BY
Silvia Oesterreich,
Federal University of Grande Dourados, Brazil
Ravi Philip Rajkumar,
Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), India

*CORRESPONDENCE
Weihong Li
✉ lwh@cdutcm.edu.cn

†These authors share first authorship

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Efficacy and safety of zuranolone in the treatment of major depressive disorder: a meta-analysis

Shuyu Wang†, Wenxing Zhang†, Zhang Liu, Tian Zhang, Yi Wang and Weihong Li*

School of Basic Medical Science, Chengdu University of Traditional Chinese Medicine, Chengdu, China

Objective: This study aimed to systematically review zuranolone's efficacy and safety in treating major depressive disorder (MDD).

Methods: We conducted electronic searches in databases like PubMed, Embase, Cochrane, and Web of Science to identify randomized controlled trials using zuranolone for severe depression from study inception to September 15, 2023. Two independent reviewers screened studies, extracted data, and assessed study quality. Our meta-analysis included four studies with 1,454 patients. The findings showed significant improvements with zuranolone across various measures: Hamilton Depression Rating Scale (HAM-D) scores indicated notable alleviation in depressive symptoms (WMD: −2.03; 95% CI: −2.42 to −1.65); the treatment group's HAM-D score response rate was significantly higher than the control group's at day 15 (OR: 1.46, 95% CI: 1.11 to 1.92, P = 0.01). The meta-analysis also revealed higher remission rates for the treatment group compared to the control group at day 15 (OR: 1.68, 95% CI: 1.18 to 2.39, P = 0.03). Additionally, HAM-A scores on day 15 and MADRS scores on day 15 showed improvement, and HAM-D scores for 30 mg zuranolone on different treatment days exhibited improvement (WMD, −2.55; 95% CI, −3.24 to −1.58; P = 0.05). However, analyzing HAM-D scores on day 15 for various zuranolone doses revealed no significant differences. Importantly, zuranolone use was associated with an increased incidence of adverse reactions.

Results: Our meta-analysis included four studies with 1454 patients, showing significant improvements with zuranolone across various measures, including HAM-D scores, HAM-A scores, MADRS scores, and specific HAM-D scores for 30 mg zuranolone on different treatment days. However, no significant differences were found in HAM-D scores on day 15 for various doses of zuranolone.

Conclusions: Our findings suggest that zuranolone is a promising, simple, and convenient treatment for patients with major depressive disorder, offering potential guidance for clinical practice.

KEYWORDS

zuranolone, SAGE-217, depression, MDD, major depressive disorder

1 Introduction

Even before the emergence of the coronavirus disease 2019 (COVID-19) pandemic, major depressive disorder (MDD) ranked among the leading global causes of health burden (Patel et al., 2016; GBD 2019 Mental Disorders Collaborators, 2022). The advent of the COVID-19 pandemic has exacerbated many determinants of poor mental health (Pirkis et al., 2021). Studies estimate an additional 53.2 million cases of MDD globally attributable to the COVID-19 pandemic (COVID-19 Mental Disorders Collaborators, 2021). MDD is one of the most common, burdensome, and costly psychiatric conditions affecting adults globally (Cipriani et al., 2018). Characterized by symptoms including a persistent depressed mood and loss of interest or pleasure in activities, among others (Shafiee et al., 2018; Köhler-Forsberg et al., 2019; Gronemann et al., 2020; Riemann et al., 2020), MDD impacts more than 3.8% of the worldwide population, marking it as a significant health issue. Recent research highlights the correlation between depression and compromised neuronal activity in key brain networks such as the central executive network (CEN), default mode network (DMN), and salience network (SN) (Yan et al., 2019). A study comparing acute and long-term outcomes within the Sequential Treatment Protocol for Depression Relief (STAR*D) trial evaluated four successive treatment steps, suggesting a theoretical cumulative response rate of 67% (Rush et al., 2006). Presently, medication stands as the primary approach to managing depression, yet antidepressants have limitations, including slow onset of action, prolonged treatment duration, and high rates of relapse. Moreover, extended use can result in diverse side effects such as sexual dysfunction, weight gain, nausea, and headaches (Moret et al., 2009). Additionally, roughly one-third of individuals with severe depression do not exhibit favorable responses to existing antidepressant medications (Daly et al., 2018). Hence, the development of new antidepressants holds critical importance as a resource for clinicians in addressing severe depression.

Zuranolone, a rapid-acting capsule taken once daily for a 14-day duration, swiftly alleviates depressive symptoms. Its effectiveness begins within 3°days, a notable improvement compared to existing treatments that might take weeks or months to show results. Notably, it stands as the first FDA-approved oral medication for postpartum depression, presenting a significant advancement over brexanolone, which is solely available as an intravenous injection administered over 60 h (equivalent to 2.5°days) (Scott, 2019). Zuranolone's once-daily capsule form provides a more accessible administration method. Operating as a neuroactive steroid (NAS) and GABA-A receptor-positive allosteric modulator (PAM), it is also indicated for severe depression. Its efficacy in treating postpartum severe depression has been established through research focused on postpartum depression.

Gamma-aminobutyric acid (GABA) plays a critical role in maintaining and restoring excitatory-inhibitory balance in the brain while regulating brain networks (Makar et al., 1975). Approximately one-third of neurons in the central nervous system (CNS) are GABAergic, responsible for regulating the function of GABAA receptors both within and outside synapses, thus restoring the balance between inhibitory and excitatory receptors in the brain (Tang et al., 2021). The GABA system serves as a key inhibitory signaling pathway in the brain and CNS and plays an important role in regulating CNS function (Koh et al., 2023). For individuals dealing with depression, zuranolone may facilitate the rapid rebalancing of misaligned neural networks to enhance overall brain function (Carvalho, 2023).

Zuranolone is recognized as a promising antidepressant agent. In clinical trials, treatment with zuranolone has demonstrated significant improvements in depressive symptoms among adults with MDD compared to a placebo, and it has generally exhibited a well-tolerated and consistent safety profile. Currently, the sample size of clinical trials for zuranolone in the treatment of MDD is limited. Therefore, further analysis of a larger dataset is necessary to comprehensively assess its efficacy and safety. Consequently, this article is based on the most recent prospective clinical trials, aiming to objectively evaluate the efficacy and safety of zuranolone in treating patients with MDD and to provide additional evidence for clinical treatment.

2 Methods

This meta-analysis was based entirely on the preferred reporting items for systematic reviews and meta-analysis (PRISMA) (Page et al., 2021), following protocols registered at the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY 20236110116).

2.1 Data sources and searches

In this study, we conducted electronic searches in English databases, primarily sourcing relevant literature from PubMed, Embase, Cochrane, and the Web of Science. The search period spanned from the inception of the databases to September 15, 2023. Two researchers (SW and ZL) independently assessed the titles and abstracts of the studies identified during the search, excluding those that were not pertinent. For the remaining studies, we thoroughly examined both the full texts and **supplementary materials** to ascertain whether they contained the necessary information. Any disagreements in the study selection process were resolved by referring to the original article and reaching a consensus with the senior investigator (WHL).

2.2 Inclusion and exclusion criteria

Inclusion criteria for MDD were as follows: (1) randomized controlled trials (RCT), (2) Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (First, 2013), and 17-item Hamilton Depression Rating Scale (HAM-D) scores (Zimmerman et al., 2013), (3) intervention: zuranolone was administered to the experimental group while the control group received a placebo (Zuranolone, 2023).

Exclusion criteria were as follows: (1) studies with inconsistent subject-object relationships, (2) studies with duplicated data, (3) unavailability of full text or complete data, and (4) studies focusing on MDD subtypes (such as severe postpartum depression or severe post-stroke depression), (5) non-English articles, and (6) publication in the form of letters, conference reports, editorials, case reports, animal studies, basic studies, or systematic reviews.

2.3 Data extraction

Endnote 21 was used for literature importation and screening. Two investigators (SW and WZ) conducted the literature screening and data extraction in accordance with the study's design, as well as the inclusion and exclusion criteria concerning the study participants. Any discrepancies that arose were resolved through discussion until a consensus was achieved. If needed, a third researcher was consulted (ZL). Data obtained from the RCTs included various parameters, including the first author, publication year, sample size, age, gender distribution, the dosage of zuranolone (50, 30, and 20 mg), treatment duration, and outcomes such as HAM-D, MADRS, and HAM-A scores, among other relevant details.

2.4 Risk-of-bias assessment

To assess study quality, we utilized the Cochrane Handbook of Systematic Reviews (Cumpston et al., 2019), employing seven key criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The risk of bias for each criterion was categorized as low, unclear, or high.

2.5 Data synthesis and statistical analysis

In this meta-analysis, we designated the HAM-D score on day 15, response and remission rate on day 15 of HAM-D as the primary outcome. The HAM-A score on day 15, the Montgomery-Asberg Depression Rating Scale (MDARS) score on day 15, and the HAM-D score for 30 mg of zuranolone on days 3, 8, and 15 as secondary endings. Additionally, we conducted subgroup analyses for different doses of zuranolone (50, 20, and 30 mg) in assessing HAM-D scores at day 15.

Heterogeneity was evaluated using the chi-square test ($P < 0.10$) and the I squared index ($I^2 > 50\%$). When both $P < 0.05$ and $I^2 > 50\%$ were met, it indicated substantial heterogeneity among the studies, leading to the adoption of a random effect model. In the analysis of overall effects, we used weighted mean difference (WMD), odds ratio (OR), and 95% confidence interval (95% CI) as the effect indicators. As the number of included studies was <10, the funnel plot and Egger's test were used to examine the potential presence of publication bias. All analyses were conducted using Comprehensive Meta-Analysis (version 4) for meta-analysis and R software (dosresmeta package version 2.0.1) for dose-response meta-analysis. A significance level of $P < 0.05$ was considered to be statistically significant.

3 Results

3.1 Literature search results

The PRISMA flowchart is presented in **Figure 1**. The initial search yielded a total of 115 relevant publications. We excluded 92 duplicate articles. Following the screening of the titles and abstracts, we excluded 12 publications. Following a comprehensive evaluation of the full texts in accordance with the inclusion and exclusion criteria, we identified four clinical trials (Gunduz-Bruce et al., 2019; Clayton et al., 2023b; Clayton et al., 2023a; Kato et al., 2023), comprising a total of 1,454 patients with MDD, for inclusion in this meta-analysis. The basic information about the included studies is shown in **Supplementary Table 1**. All the participants were diagnosed with MDD through a combination of DSM criteria and HAM-D scores. They were administered either oral zuranolone or a placebo once daily. A detailed quality assessment of the included literature is presented in **Supplementary Table 1**.

3.2 Primary outcomes

3.2.1 HAM-D score on day 15

The meta-analysis results showed that the HAM-D scores in the treatment group were significantly higher than those in the control group at day 15 (WMD, −2.03; 95% CI, −2.42 to −1.65; $P < 0.001$). The heterogeneity was low ($\chi 2 = 21.43$; $P = 0.09$; $I^2 = 35.0\%$). The results are shown in **Figure 2A**. The funnel plot (in **Figure 2B**) shows a visual assessment of potential publication bias. Egger's test showed that the results were not significantly affected by publication bias ($t = -3.06$; $P = 0.0092$).

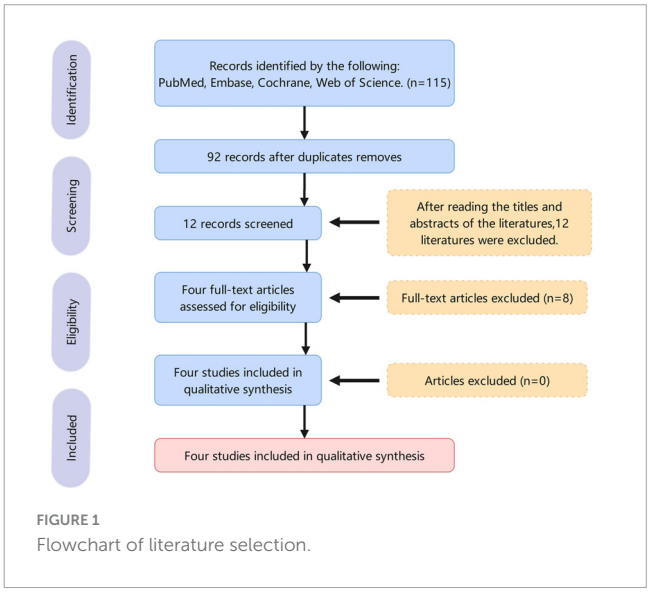

FIGURE 1
Flowchart of literature selection.

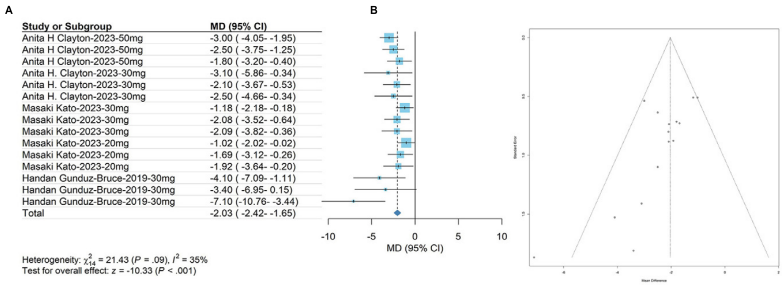

FIGURE 2
(A) denotes the HAM-D score on day 15; **(B)** denotes the funnel plot.

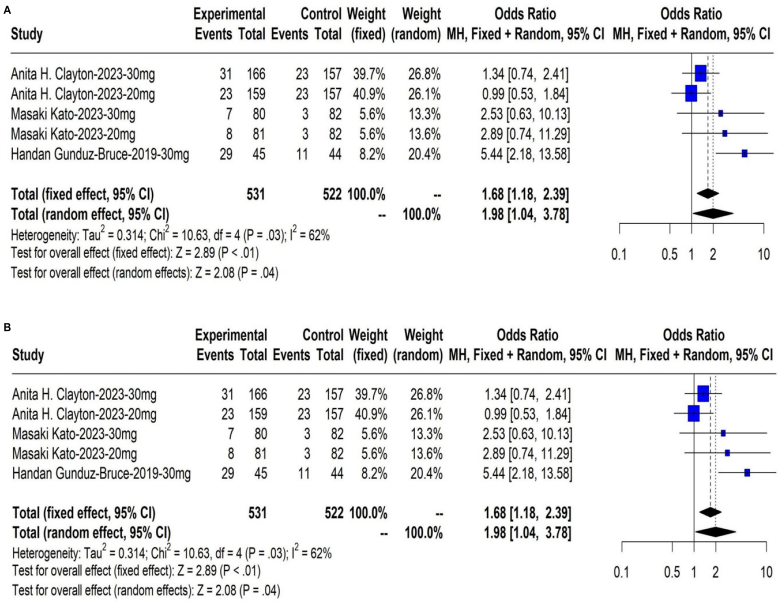

FIGURE 3
(A) The response rate on day 15 of HAM-D score; **(B)** The remission rate on day 15 of HAM-D score.

3.2.2 Response and remission rate on day 15 of HAM-D score

The meta-analysis results showed that the response rate of HAM-D score in the treatment group were significantly higher than those in the control group at day 15 (OR: 1.46, 95% CI: 1.11 to 1.92, $P < 0.01$). The results are shown in Figure 3A. The meta-analysis results showed that the remission rate of HAM-D score in the treatment group were significantly higher than those in the control group at day 15 (OR: 1.68, 95% CI: 1.18 to 2.39, $P < 0.01$). The results are shown in Figure 3B.

3.3 Secondary outcomes

3.3.1 HAM-A score on day 15

The meta-analysis results showed that changes in HAM-A scores on day 15 in the group receiving zuranolone were significantly higher than those in the control group (WMD, −1.08; 95% CI, −1.80 to −0.37; $P = 0.003$). The heterogeneity was low ($\chi 2 = 6.48$; $P = 0.09$; $I^2 = 54.0\%$). Egger's test showed that the results were not significantly affected by publication bias ($t = -1.58$; $P = 0.2546$). The results are shown in Figure 4A.

3.3.2 Montgomery-Asberg depression rating scale score on day 15

The meta-analysis results showed that the Montgomery-Asberg Depression Rating Scale (MDARS) score in the treatment group was significantly higher than that in the control group on day 15 (WMD, −2.71; 95% CI, −4.29 to −1.14; $P < 0.001$). The heterogeneity was low ($\chi 2 = 3.54$; $P = 0.17$; $I^2 = 43.0\%$). Egger's test showed that the results were not significantly affected by publication bias ($t = -2.35$; $P = 0.2560$). The results are shown in Figure 4B.

3.4 Subgroup analyses

Subgroup analyses of the primary outcomes were conducted, and the results showed that most subgroups yielded consistent

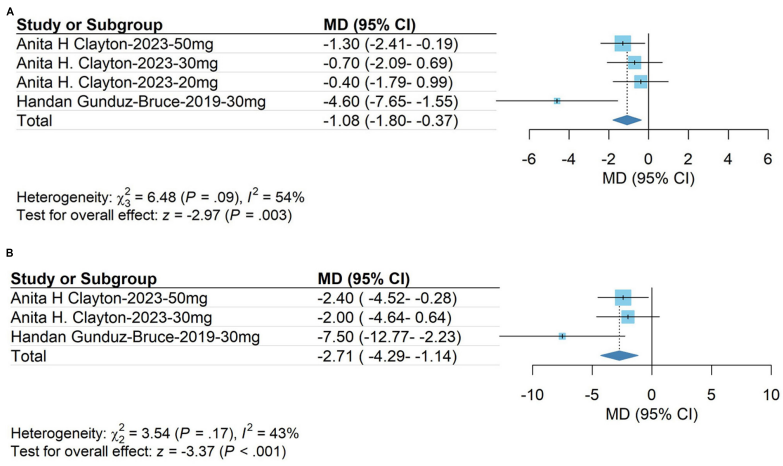

FIGURE 4
(A) HAM-A score on day 15; **(B)** Montgomery-Asberg Depression Rating Scale (MDARS) score on day 15.

results. There were no significant differences among the subcategories within each subgroup.

3.4.1 HAM-D score of 30 mg zuranolone on days 3, 8, and 15

The subgroup analysis for the 30 mg zuranolone dosage yielded the following outcomes: WMD, −2.55; 95% CI, −3.24 to −1.58; P = 0.05; I^2 = 35%; fixed model. The meta-analysis demonstrated alterations in zuranolone's HAM-D score at day 3 (WMD, −2.55; 95% CI, −3.20 to −1.00; $P < 0.01$; I^2 = 66%; fixed model), changes in zuranolone's HAM-D score at day 8 (WMD, −2.17; 95% CI, −2.86 to −1.48; $P < 0.01$; I^2 = 0%; fixed model), and modifications in zuranolone's HAM-D score on day 15 (WMD, −2.47; 95% CI, −3.64 to −1.29; $P < 0.01$; I^2 = 46%; fixed model). These results are shown in Figure 5.

3.4.2 HAM-D score on day 15 for zuranolone doses of 20, 30, and 50°mg

The dose of zuranolone was categorized into three groups: 50, 20, and 30 mg (HAM-D scores on day 15). Subsequently, the dose of zuranolone was analyzed within these subgroups (WMD, −2.55; 95% CI, −3.24 to −1.58; P = 0.05; I^2 = 35%; fixed model). The meta-analysis results showed changes in HAM-D scores in the 50 mg zuranolone group on day 15 (WMD, −3.49; 95% CI, −2.65 to −1.64; P = 0.05; I^2 = 0%). Additionally, changes in HAM-D scores in the 20 mg zuranolone group on day 15 (WMD, −1.37; 95% CI, −2.10 to −0.63; $P < 0.01$; I^2 = 0%, fixed model) and changes in HAM-D scores in the 30°mg zuranolone group on day 15 (WMD, −2.43; 95% CI, −3.28 to −1.58; $P < 0.01$; I^2 = 40%; fixed model). The results are shown in Figure 6.

3.5 Adverse events during the treatment period

The incidence rates of adverse reactions with zuranolone compared to placebo, ranked from highest to lowest, were as follows: dizziness at 3.05% (95% CI: 1.98 to 4.70), somnolence at 2.89% (95% CI: 1.94 to 4.31), sedation at 2.85% (95% CI: 1.57 to 5.19), headache at 1.32% (95% CI: 0.93 to 1.87), and diarrhea at 0.81% (95% CI: 0.50 to 1.32). Utilizing a fixed-effects model in a meta-analysis, a statistically significant discrepancy in adverse reaction occurrence rates emerged between the treatment and control groups (OR: 1.92, 95% CI: 1.59 to 2.32, $P < 0.01$). The results of the adverse reaction occurrence rates are shown in Figure 7, indicating an increased probability of adverse reactions following zuranolone administration.

3.6 Sensitivity analysis

Sensitivity analysis was performed on the HAM-D scores and the clinical efficacy of the zuranolone intervention for MDD. The sensitivity analyses indicated the robustness of all the findings. Consequently, one article was excluded, and a meta-analysis was conducted on the remaining articles. The combined results from the remaining studies remained statistically significant, underscoring the robustness of the findings and confirming that the exclusion had no impact on the final results. The results are presented in Supplementary Figure 1.

4 Discussion

Zuranolone afforded better efficacy than a placebo in HAM-D, HAM-A, and MDARS scores, and depressive response and remission rates. Notably, while HAM-A and MDARS scores exhibited improvement by day 15 compared to baseline, they displayed high heterogeneity due to missing scores on other treatment days in the clinical trial, precluding subgroup analysis. Consequently, our focus shifted to HAM-D scores on day 15 for subgroup analysis across zuranolone doses of 50, 20, 30, and 30 mg on various treatment days. Results indicated a delayed effect with the 20 mg dose, while no significant difference emerged between 30 and 50 mg, suggesting a plateau effect with increased dosage.

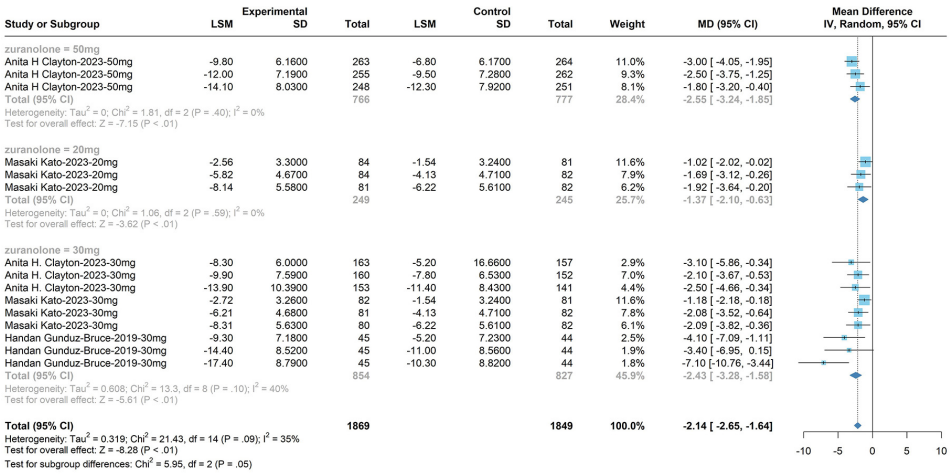

FIGURE 5
Hamilton Depression Rating Scale (HAM-D) score of 30 mg zuranolone on days 3, 8, and 15.

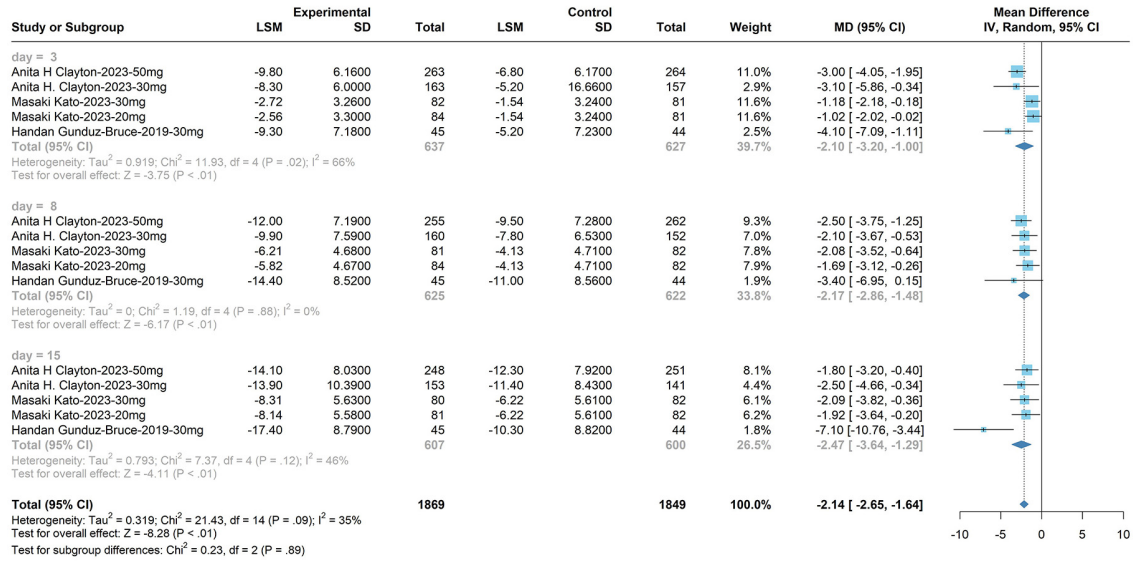

FIGURE 6
The dose of zuranolone was categorized into three groups: 50, 20, and 30 mg (HAM-D scores on day 15).

Moreover, the 30 mg dose manifested rapid effectiveness on day 3, maintaining efficacy on days 8 and 15.

Additionally, a study (Clayton et al., 2023b) reported positive responses among patients in the zuranolone treatment group on day 15, maintaining an average of 86.1% improvement in HAM-D-17 on day 42 (4°weeks post-treatment). This underscores the need for further investigation into zuranolone's long-term antidepressant effects and duration in future trials. Regarding adverse events, zuranolone showed an increased an incidence compared to placebo. Common adverse reactions encompassed dizziness, somnolence, sedation, headaches, and diarrhea. Literature (Kato et al., 2023) also reports occurrences of infection and invasion, rhinitis, neurological and gastrointestinal disorders, and skeletal diseases associated with zuranolone.

One of the earliest suggested biological mechanisms underlying MDD involves deficiencies in monoamine levels, such as 5-HT, noradrenaline, and dopamine (Hamon and Blier, 2013). The molecular mechanisms of MDD remain poorly understood. Studies have indicated that functional differences observed in fibroblasts derived from patients with MDD persist to some extent after reprogramming into induced NPCs, potentially linked to altered functioning of iPS neurons and thus possibly associated with the etiology of MDD (Fries et al., 2023). Furthermore, studies have revealed that MDD is associated with disruptions in various neurotransmitters within the brain, cerebrospinal fluid, and peripheral tissues (Pan et al., 2018), including imbalances in GABA (Fogaça and Duman, 2019).

Zuranolone is a neuroactive steroid (NAS) that acts as a positive allosteric modulator (PAM) of the GABAA receptor.

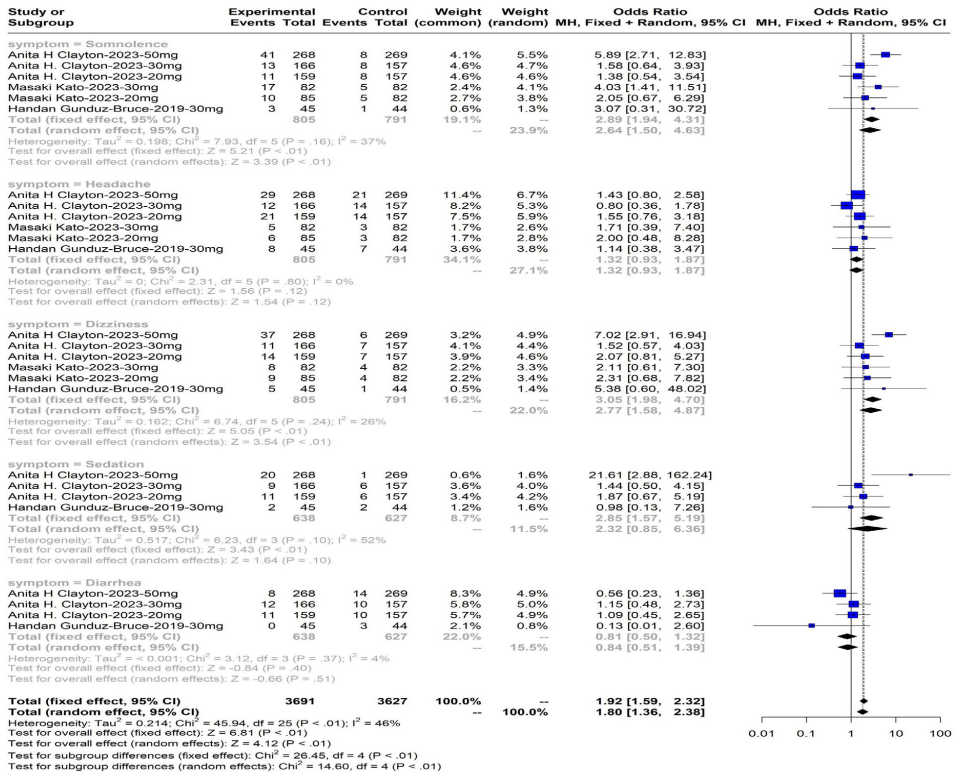

FIGURE 7
Adverse events.

GABA, a naturally occurring non-protein amino acid, serves as a vital inhibitory neurotransmitter in the mammalian CNS, with approximately 30% of the CNS synapses utilizing GABA as a transmitter. GABA plays an important role in various regions of the human brain, including the human cerebral cortex, hippocampus, thalamus, basal ganglia, and cerebellum, exerting regulatory influence on a variety of cognitive functions. Zuranolone is believed to function by restoring balance to brain networks responsible for critical functions like mood, arousal, behavior, and cognition. When GABA levels are deficient in the human body, it can lead to the manifestation of emotions such as anxiety, restlessness, fatigue, and worry. Zuranolone plays a role in helping to restore the proper functioning of dysfunctional GABAA receptors, potentially ameliorating these symptoms.

The study has several limitations. First, some of the included studies did not clearly report blinding and allocation concealment, which may have introduced heterogeneity. Second, in future research, it would be beneficial to include more studies in subgroup analysis to further validate the conclusions drawn in this study. Third, the limited number of original studies available for inclusion in this analysis increases the risk of false-positive results. Fourth, the published randomized controlled trials lacking the efficacy of zuranolone versus other antidepressants are still lacking in the literature, and subsequent research work should be aimed at addressing this. Given the limitations of these studies, multicenter, large-sample, double-blind, high-quality randomized controlled studies are needed to provide a higher level of evidence.

Zuranolone has received fast-track and breakthrough therapy designations from the FDA for treating MDD. Despite conducting three phase III clinical trials focusing on MDD, the MOUNTAIN study failed to meet the primary clinical endpoint of the Hamilton Depression Rating Scale assessment, showing only a 1.3 improvement compared to placebo, falling short of the generally considered clinically meaningful level of depression, set at 1.5. The WATERFALL study did achieve the primary clinical endpoint but exhibited only a 1.7 improvement compared to placebo. These trial outcomes, along with safety concerns raised by the FDA, included reports of suicidal ideation and behavior in clinical MDD studies. Regarding safety issues, Sage spokesman Matthew Henson mentioned that these concerns were associated with patients receiving the oral solution of Zurzuvae, not the approved capsule formulation. Henson emphasized the absence of reports regarding loss of consciousness among participants in studies for PPD and MDD. In reviewing the new FDA documents, RBC Capital Markets analyst Brian Abrahams highlighted an incident where a patient with MDD showed no response to stimuli for up to 50 min after receiving a high dose of Zurzuvae. Notably, this patient had taken a dose exceeding the currently approved dosage by 30 to 50%, experiencing loss of consciousness twice, while another subject experienced nearly 5°h of unconsciousness.

Despite these limitations, the quantitative meta-analysis of zuranolone in the treatment of MDD exhibited good result stability in sensitivity analysis. Furthermore, this study contributes to our understanding of the efficacy and safety of zuranolone intervention for MDD, highlighting improvements in the depressive state for patients with MDD.

Failure in clinical trials does not necessarily equate to failure in a drug's potential indication. Clinical setbacks often stem from

trial design or patient population. Adjustments in these areas can sometimes lead to the reintroduction of a clinically unsuccessful drug to the market. Numerous examples in various fields of drug development attest to this. In the case of Zuranolone for MDD, Sage remains in ongoing discussions with the FDA. Even if a drug is not ultimately deemed suitable for a particular indication, it does not signify complete failure, as there might be prospects for its use in other indications. Despite these limitations, the quantitative meta-analysis of zuranolone for severe depression demonstrates consistent and stable results in sensitivity analysis. This study significantly contributes to our understanding of the efficacy and safety of intervening with MDD, highlighting its efficacy in alleviating depressive symptoms among patients with MDD.

Data availability statement

The original contributions presented in this study are included in this article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

Author contributions

WL designed the study. SW and WZ performed the search and analysis. ZL, YW, and TZ checked the analyzed the data. SW wrote the manuscript in consultation with WZ, ZL, YW, and TZ. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2023.1332329/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Sensitivity analysis.

SUPPLEMENTARY FIGURE 2
Risk of bias summary.

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EDITED BY
Anna Tabęcka-Łonczynska,
University of Information Technology and Management in Rzeszow, Poland

REVIEWED BY
Kamila Rybczyńska-Tkaczyk,
University of Life Sciences of Lublin, Poland
Przemyslaw Solek,
Medical University of Lublin, Poland

*CORRESPONDENCE
Yaoheng Lu,
lyh93@cdutcm.edu.cn
Ying Xiong,
61711445@qq.com

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Chinese herbal medicines for the treatment of depression: a systematic review and network meta-analysis

Chun Dang[1], Qinxuan Wang[2], Qian Li[3], Ying Xiong[1]* and Yaoheng Lu[4]*

[1]Department of Periodical Press, West China Hospital, Sichuan University, Chengdu, China, [2]West China School of Medicine, Sichuan University, Chengdu, China, [3]Department of Neurology, The Second Affiliated Hospital of Harbin Medical University, Harbin, China, [4]Department of General Surgery, Chengdu Integrated Traditional Chinese Medicine and Western Medicine Hospital, Chengdu, China

Objectives: Amidst rising global burden of depression and the associated challenges with conventional antidepressant therapies, there is a growing interest in exploring the efficacy and safety of alternative treatments. This study uses a Bayesian network meta-analysis to rigorously evaluate the therapeutic potential of Chinese herbal medicines in the treatment of depression, focusing on their comparative efficacy and safety against standard pharmacological interventions.

Methods: Five databases (PubMed, Wanfang Data, EMBASE, CNKI, and the Cochrane Library) and grey literature were searched from inception to end of July 2023 to identify studies that assessed the efficacy and safety of Chinese herbal medicines in treating depression. The response rate, Hamilton Depression Scale (HAMD) scores, and rates of adverse events were assessed through both direct and indirect comparisons. Data extraction and risk of bias assessment were meticulously performed. Statistical analysis used Markov chain Monte Carlo methods, with effect size estimates provided as odd ratios and their 95% confidence intervals.

Results: A total of 198 RCTs involving 8,923 patients were analyzed, assessing 17 Chinese herbal medicines. Surface Under the Cumulative Ranking results indicated that the top three treatments with the best response rate were possibly *Guipiwan*, *Ease Pill*, and *Chaihu Jia Longgu Muli Decoction*; the top three treatments on the reduction of HAMD scores were *Chai Hu Shu Gan San*, *Xingnao Jieyu Decoction*, and *Xiaoyao Powder*; and the top three treatments with the lowest adverse effects rates were *Xiaoyao Powder*, *Alprazolam*, and *Xingnao Jieyu Decoction*. Interestingly, commonly used synthetic drugs such as *Fluoxetine*, *Escitalopram*, *Amitriptyline*, *Sertraline*, *Flupentixol and Melitracen*, and *Venlafaxine*, not only appeared to be less effective than specific Chinese herbal medicines (*Gan Mai Da Zao Decoction*, *Chaihu Jia Longgu Muli Decoction*, *Chai Hu Shu Gan San*, *Danzhi-Xiaoyao-San*, and *Xingnao Jieyu Decoction*), but they were also related to substantially higher risk of adverse events.

Conclusion: Our findings elucidate the promising therapeutic potential of Chinese herbal medicines as viable alternatives in the treatment of depression, with certain herbs demonstrating enhanced efficacy and safety profiles. The outcomes of this study advocate for the integration of these alternative modalities

into contemporary depression management paradigms. However, it underscores the necessity for larger, methodologically robust trials to further validate and refine these preliminary findings.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/, identifier CRD42023452109.

KEYWORDS

bayesian network meta-analysis, Chinese herbal medicine, depression, treatment, antidepressant

Introduction

Depression is a pervasive mental disorder that causes people to experience anhedonia (Monroe and Harkness, 2022). Depression symptoms include sadness, cognitive difficulties, which reduce patients' quality of life and social functioning (Bosc, 2000). Depression impacts approximately 3.8% of the global population. Its prevalence is notably higher in the adult demographic, affecting about 5% of this group. According to the World Health Organization, an estimated 280 million adults across the globe are afflicted with this condition (Freitas et al., 2023).

In the pharmacotherapeutic management of depressive disorders, a diverse array of antidepressant classes is employed. These include Tricyclic Antidepressants, Selective Serotonin Reuptake Inhibitors (SSRIs), Monoamine Oxidase Inhibitors, Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs), Noradrenaline Reuptake Inhibitors, and Noradrenaline and Dopamine Reuptake Inhibitors. These pharmacological agents primarily function by inhibiting the transporters implicated in the reuptake of monoamines, a mechanism crucial in the modulation of mood and affective states (Dobrek and Głowacka, 2023). Additionally, several other compounds exhibit antidepressant properties. For instance, *agomelatine* acts as an MT1 and MT2 melatonin receptor agonist and a serotonin 5HT2 receptor antagonist, while *mirtazapine* is known to antagonize adrenergic alpha2-autoreceptors, alpha2-heteroreceptors, as well as 5-HT2 and 5-HT3 receptors. More recent developments in antidepressant pharmacotherapy include agents such as desvenlafaxine, vortioxetine, and vilazodone (Fournier et al., 2010; Faquih et al., 2019).

The therapeutic efficacy of antidepressants demonstrates considerable variability across the patient population. SSRIs and SNRIs are frequently prioritized as first-line treatments, owing to their favorable safety profiles and high tolerability. Empirical studies indicate that approximately 60%–70% of individuals diagnosed with depression experience a notable improvement in symptoms following their initial course of antidepressant therapy. Symptom amelioration can often be observed within a span of several weeks. However, there remains a substantial proportion, estimated at 30%–40%, who may not exhibit an adequate response to their first prescribed medication. This subset of patients may necessitate alterations in their pharmacological regimen or the incorporation of adjunctive therapeutic approaches (Irfan, 2024).

In addition, there are numerous adverse effects are caused by modern pharmacological drugs. The adverse effects of selective SSRIs include QT prolongation, serotonin syndrome, insomnia, rashes, and hyponatremia, whereas long-term use may lead to sexual dysfunction and weight gain (Goethe et al., 2007; Nachimuthu et al., 2012). Additionally, Monoamine Oxidase Inhibitors and Serotonin Reuptake Inhibitors are associated with potentially serious reactions such as hypertensive crisis, and increased risk of suicidal ideation (Sathyanarayana Rao and Yeragani, 2009; Nobile et al., 2019; Mrozek et al., 2023). Furthermore, overdoses of tricyclic antidepressants can precipitate severe cardiac complications, including sudden heart attack, tachycardia, and ventricular fibrillation (Scala et al., 2023; Yildiz et al., 2023).

In recent years, herbal medicines are gaining interests and recognitions (Saxena et al., 2023). Numerous Chinese herbal medicines have been investigated for their potential antidepressant effects (Garg et al., 2023). Various Chinese herbal medicines have been reported to have excellent antidepressant effects compared with current synthetic pharmaceuticals, such as *Morinda Officinalis Oligosaccharide Capsule*, *Guipiwan*, *Jieyu Decoction*, *Shugan Jieyu Capsule*, *Wuling Capsule*, *Ease Pill*, *Yangxue Qingnao Granule*, *Yueju Pill*, *Buyang Huanwu Decoction*, *Chaihu Jia Longgu Muli Decoction*, *Chai Hu Shu Gan San*, *Danzhi-Xiaoyao-San*, *Gan Mai Da Zao Decoction*, *Huoxue Soup Decoction*, *Wendan Anshen Decoction*, *Xiaoyao Powder*, and *Xingnao Jieyu Decoction* (Holden, 1987; Yeung et al., 2014a; Peng et al., 2014; Zhang et al., 2014; Feng et al., 2016; Kwon et al., 2018; Zhen et al., 2022).

The pharmacodynamic mechanisms on herbal medicines in treatment of psychiatric disorders are multifaceted. Primarily, these mechanisms encompass the modulation of neuronal communication. This is achieved through the binding of specific plant-derived metabolites to neurotransmitter and neuromodulator receptors (Sarris et al., 2011). Additionally, these herbal compounds can influence neurotransmitter synthesis and overall neurological function (Sarris, 2007). Beyond these neural interactions, herbal medicines may exert their therapeutic effects by either stimulating or sedating central nervous system activity. They also play a role in regulating and supporting the healthy functioning of the endocrine system (Kumar, 2006).

Previous published studies have only compared single Chinese herb medicine, without comparisons of multiple Chinese herb medicines. Therefore, the efficacy, tolerability, or safety is not possible to ascertain on various Chinese herb medicines. In this study, we chose common Chinese herbal medicines for depression treatment. This study rigorously evaluates specific aspects on efficacy (as measured by Hamilton Rating Scale for Depression (HAMD) score and response rate) and safety (adverse effects rate) in the context of therapeutic approaches for depression. The HAMD score is the foremost clinician-rated scale used for assessing depression severity in patients diagnosed with depressive

disorders (Carrozzino et al., 2020). The response rate, defined as a reduction of ≥50% in HAMD scores at the study endpoint, is a validated and commonly employed measure of depression severity (McIntyre et al., 2005). Adverse effects rate, quantifying the proportion of patients experiencing at least one adverse event relative to the total number of patients in the intervention or control group, is a widely accepted metric for evaluating safety (Weibel et al., 2020; Dean et al., 2021; De Crescenzo et al., 2022).

Thus, this Bayesian network meta-analysis aims to synthesize and assess the existing available evidence for the efficacy and safety of various Chinese herbal medicines for the treatment of depression.

Methods

This network meta-analysis was registered in PROSPERO with accession number CRD42023452109. The protocol followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocol (Moher et al., 2015). The time of registration occurred was 17 May 2023. There are not any modifications about the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocol during the study. The researchable question was performed using the PICOS (Population, Intervention, Comparison, Outcome, Study design) format. Population: patients with depression. Intervention: participants received Chinese herbal medicines. Comparison: participants received modern pharmacological antidepressants, placebo, or no-treatment. Outcome: HAMD scores, the response rate, and the incidence of drug-related adverse reactions. Study design: randomized controlled trials (RCTs).

Data searches

A systematic literature search for articles was performed in PubMed, Wanfang Data, EMBASE, CNKI, and the Cochrane Library. Grey literature was also searched. Articles were searched in English or Chinese from inception through the end of July 2023 for studies that assessed the efficacy and safety of Chinese medicines with depression. The detailed search strategy and search terms are shown in Supplementary Appendix S1.

Study selection

Two review authors (Chun Dang and Yaoheng Lu) independently screened the titles and abstracts, and differences were resolved through discussion and consensus agreement. Studies which potentially fulfilled the inclusion and exclusion criteria were identified, then full-text reviews were performed.

Inclusion criteria

The inclusion criteria were as follows: (1) Adult patients (≥18 years) with depressive symptoms were eligible. Depression was defined by the standardized diagnostic manuals (Blatch Armon, et al., 2023), such as the Diagnosis and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) or later versions (Hasin et al., 2006), the International Classification of Diseases, 10th Edition (ICD-10) (Herrmann et al., 1998), the Chinese Classification of Mental Disorders, Third Edition (CCMD-Ⅲ) or later versions. (2) The intervention group received common Chinese herbal medicines, while the control group received current synthetic pharmaceuticals, placebo, or no-treatment. All forms of Chinese herbal medicines (i.e., decoctions, formula, capsules, pills, and powders) were included. Current synthetic pharmaceuticals (i.e., *Fluoxetine*, *Escitalopram*, *Amitriptyline*, *Maprotiline*, *Venlafaxine*, *Paroxetine*, *Venlafaxine*) were included. Participants who were only assigned one drug without the combination of different antidepressants or non-pharmacology treatments (i.e., cognitive-behavioral therapy, psychotherapy). (3) Outcome included HAMD scores, the clinical response rate, and the incidence of drug-related adverse reactions. (4) Only RCTs were included.

Exclusion criteria

The exclusion criteria were as follows: (1) Treatment groups using combinations of other depression drugs; (2) Studies with missing data about HAMD scores, or the total clinical response rate. (3) Studies that were not RCTs.

Data extraction

Two review authors (Chun Dang and Yaoheng Lu) independently extracted the data from the included studies, resolving disagreements through consensus agreement or with third-party reviewers (Qian Li). We extracted data on patients' characteristics (age, gender, numbers, comorbidity), interventions and control group (trial groups, duration, administration), outcomes (HAMD scores, the total clinical response rate in baseline and post-treatment), and adverse events. Due to the lengthy nature of the drug names, they have been abbreviated for enhanced readability and improved visual presentation in the figures and tables.

When discrepancies were identified, the primary reviewers discussed them to reach a consensus. If the primary reviewers cannot resolve a discrepancy, a third-party reviewer is consulted. The third-party reviewer provided an independent assessment of the disputed data points. Blinding was used during the data extraction process.

Study quality assessment

Due to the inclusion of RCTs in this study, we have used the Cochrane Collaboration's recommended bias assessment tool, ROB 2.0, specifically designed for RCTs. ROB is widely recognized and extensively used as the predominant tool for assessing bias risk in RCTs (Higgins et al., 2011). The risk of bias was assessed in terms of the five domains: (1) Risk of bias arising from the randomization process; (2) Missing outcome data; (3) Risk of bias due to deviations from the intended interventions; (4) Risk of bias in the selection of

the reported result; (4) Risk of bias in the measurement of the outcome. The risk of bias was graded as "low risk of bias", "some concerns" and "high risk of bias". All stages were independently performed by two authors (Chun Dang and Yaoheng Lu).

Statistical analysis

In this study, which involves the comparison of multiple different interventions and includes a significant number of indirect comparisons, we have adopted the commonly used Markov chain Monte Carlo method (MCMC). This approach utilizes a random effects generalized linear model for Bayesian network meta-analysis (Jansen et al., 2008). The nma. fit () function is adept at performing model fitting and identifying potential outliers. The lever plots and Deviance Information Criterion (DIC) values generated by this function are instrumental in determining the most suitable effect model. The lever diagram illustrates the comparison between leverage_ik (leverage for test i in arm k) and Bayesian deviation residuals for all I tests across each of the K arms. This diagram is particularly useful for highlighting potential outliers in model fitting. Specifically, if a data point falls outside the purple arc, it may indicate poor model fitting. We used odd ratios or their logarithms as the effect index of counting data and their 95% confidence intervals (*CI*) as limits. We use mean difference as the statistical effect size for continuous variables, and OR for binary variables, based on the type of outcome data. When the odds ratio (*OR*) value did not contain 1 at the 95% *CI*, the difference was considered statistically significant. Statistical heterogeneity was assessed using the I^2 statistic (Chen and Benedetti, 2017). The I^2 statistic for assessing statistical heterogeneity, serves as a method to measure the degree of variance among multiple study effects. It specifically quantifies the percentage of total variation that is attributable to differences between studies, rather than to sampling error. The categorization of heterogeneity via the I^2 statistic is as follows: I^2 of 0 indicates that the variation among studies is solely due to sampling error; I^2 between 0.25 and 0.5 suggests moderate heterogeneity; and I^2 greater than 0.5 is indicative of high heterogeneity. Some scholars argue that the I^2 statistic, by applying a degrees-of-freedom adjustment, mitigates the impact of the number of included studies on the Q value, ensuring that its magnitude does not fluctuate with the number of studies and thus making the heterogeneity test results more robust and reliable (Higgins et al., 2003). The magnitude of publication bias is assessed by examining the distribution of individual study points within a funnel plot. If the points are symmetrically distributed on either side of the plot, it suggests a lower likelihood of publication bias. The convergence of the model was performed using the Gelman-Rubin method combined with a density plot and tractory plot (Brooks and AJJCGS, 1998). A network meta-analysis was performed for each collected outcome of studies. For different outcomes, we summarized the current evidence by drawing three network graphs. The effectiveness, and safety of different drugs in the treatment of depression were ranked based on the Surface Under the Cumulative Ranking (SUCRA) curve (Salanti et al., 2011). Pairwise meta-analysis will be conducted using Stata, version 17, and network meta-analysis within the Bayesian framework will be conducted by using R software, version 4.3.1 (R Foundation for Statistical Computing, Shanghai, Asia), with the package calling "gemtc 0.8–2" and "JAGS" (version 3.5.3) (Neupane et al., 2014; Shim et al., 2019). $p < 0.05$ was considered to indicate statistical significance.

Results

Screening results

After database retrieval, 8,923 citations were identified in five databases and 538 studies in the grey literature. Ultimately, 198 randomized control trials fulfilled the inclusion and exclusion criteria after reading the full text (Figure 1).

Study and participant characteristics

The analysis incorporated 198 RCTs, which collectively enrolled 8,923 patients. These patients were treated with 17 Chinese herbal medicines for depression treatment. This study included six trials (646 patients) on *Morinda Officinalis Oligosaccharide Capsule*, two trials (92 patients) on *Guipiwan*, 18 trials (690 patients) on *Jieyu Decoction*, 35 trials (1,469 patients) on *Shugan Jieyu Capsule*, 15 trials (697 patients) on *Wuling Capsule*, five trials (187 patients) on *Ease Pill*, two trials (152 participants) on *Yangxue Qingnao Granule*, three trials (98 patients) on *Yueju Pill*, eight trials (326 patients) on *Buyang Huanwu Decoction*, 34 trials (1,601 patients) on *Chaihu Jia Longgu Muli Decoction*, 11 trials (391 patients) on *Chai Hu Shu Gan San*, 19 trials (834 patients) on *Danzhi-Xiaoyao-San*, 12 trials (382 patients) on *Gan Mai Da Zao Decoction*, 12 trials (644 patients) on *Huoxue Soup Decoction*, five trials (227 patients) on *Wendan Anshen Decoction*, seven trials (248 patients) on *Xiaoyao Powder*, and four trials (239 patients) on *Xingnao Jieyu Decoction*. The median follow-up period for these trials ranged from 4 weeks to 6 months. All studies were conducted in China. A detailed description of the participants is presented in Supplementary Table S1 (Cao and Zhong, 2008; Cao, 2009; Chang and Wang, 2010; Chen and Bai, 2011; Chen and Wang, 2012; Qu et al., 2012; Cao and Chi, 2017; An and Wang, 2019; Chen GXFN. and Li T., 2009; Chen KZC. and Li XX., 2009; Chen and He, 2009; Chen and Wang, 2009; Deng and Sun, 2012; Du and Yu, 2012; Chen and Dou, 2014; Chen and Wang, 2015; Ding, 2015; Chen and Ma, 2016; Cheng and Yang, 2016; Chen and Li, 2017; Chen and Zhang, 2018; Cheng and Li, 2020; Deng et al., 2022; Gong, 2010; He, 2011; Gao et al., 2012; Guo et al., 2012; Feng, 2013; Guan and Wu, 2014; Guo and Hu, 2014; Huang and Ting, 2014; Guo and Zhang, 2015; Guan et al., 2017; He et al., 2017; Guo et al., 2018; He and Wang, 2018; Hou and Wang, 2019; Guo and Li, 2020; Li and Zhang, 2004; Huang et al., 2007; Li and Li, 2008; Jing et al., 2009; Li et al., 2009; Li and Zhang, 2010; Li and Zhao, 2011; Li RGZT. and Li S., 2012; Li SHLY. and Li SS., 2012; Huang and Zhou, 2014; Li and Li, 2014; Jiao et al., 2015; Li and Gao, 2015; Li QLLJ. et al., 2016; Li SSYM. et al., 2016; Jin et al., 2017; Lai and Yi,

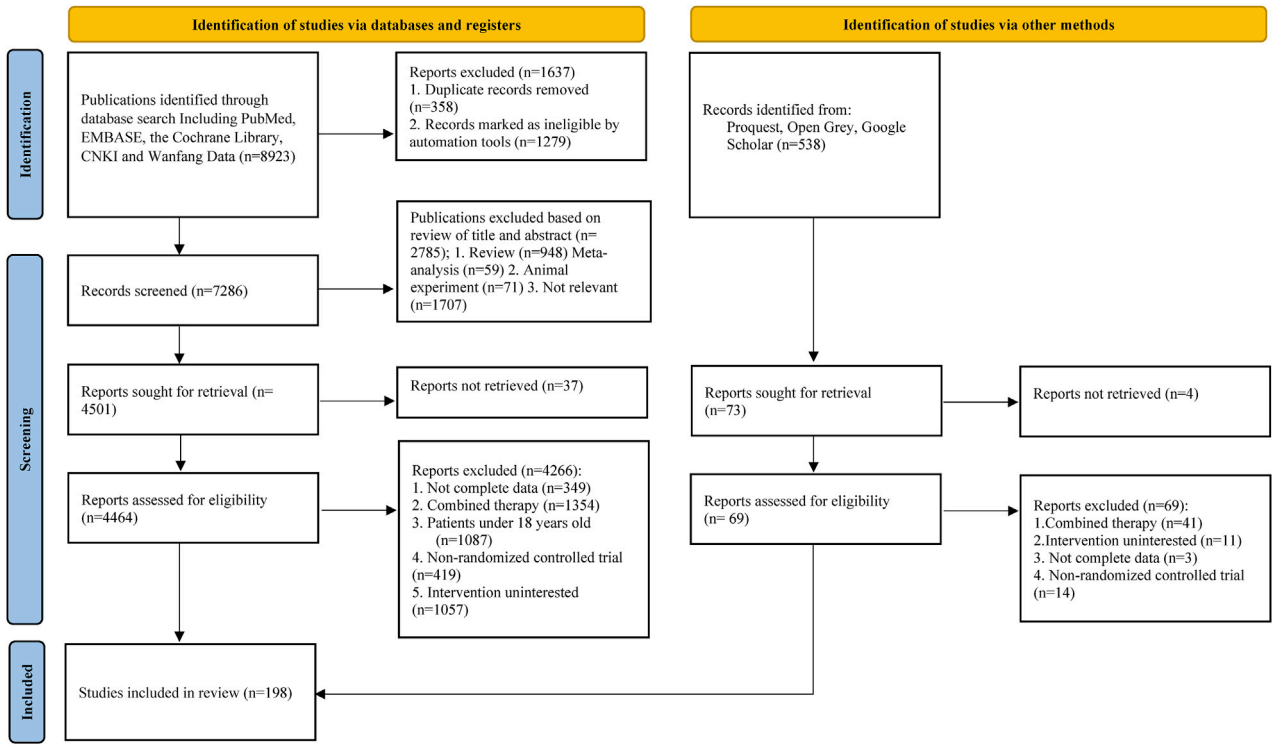

FIGURE 1
Supplementary Figure S1 Search results and study selection. This flow diagram adapted from PRISMA depicts the search results retrieved from databases and illustrates the process of literature screening.

2017; Li and Guo, 2017; Jia et al., 2019; Li and Wang, 2019; Li et al., 2003; Li and Wang, 2004; Li, 2007; Li and Qian, 2007; Liu et al., 2007; Li and Tian, 2008; Li and Dong, 2009; Li et al., 2010; Liu and Tan, 2010; Lin et al., 2011; Liu and Zhang, 2012; Li and Luo, 2013; Li et al., 2014; Li and Wang, 2015; Liu and Wang, 2015; Liu and Wang, 2017; Li et al., 2018; Lin and Han, 2019; Liu and Wang, 2019; Li et al., 2020; Luo and Zhao, 2006; Meng et al., 2008; Mao and Li, 2010; Ran et al., 2010; Meng and Li, 2011; Qiu and Zhu, 2011; Qu et al., 2011; Mao and Li, 2016; Meng et al., 2016; Nie et al., 2016; Qin and Tang, 2016; Ma and Ye, 2017; Qi et al., 2017; Ren, 2017; Min CX and Li, 2018; Lu and Li, 2019; Luo et al., 2019; Lu and Xin, 2020; Luo and Wu, 2021; Lu and Sun, 2022; Shen and Zhao, 2004; Tao and Li, 2006; Shi and Zeng, 2008; Ta et al., 2008; Tang and Wang, 2009; Shao and Zhao, 2011; Wang and Wang, 2011; Sun and Li, 2012; Sun and Zhou, 2012; Tao and Yin, 2012; Ren and Li, 2015; Tan et al., 2015; Tao and Wang, 2015; Shao and li, 2016; Tu and Wang, 2016; Wang et al., 2016; Wang and Wang, 2018; Song and Li, 2019; Wang and Li, 2019; Wang and Shao, 2019; Wang and Ma, 2006; Wang and Luo, 2007; Wang and Wu, 2008; Wang and Shu, 2009; Wang and Ban, 2010; Wang et al., 2012; Wang et al., 2014; Wei and Huang, 2014; Wei and Lu, 2014; Wang and Liu, 2016; Wang and Yang, 2016; Wu and Zhu, 2016; Wang and Li, 2017; Wang and Liu, 2017; Wang and Dou, 2018; Wang and Zhang, 2018; Wang and Zhang, 2019; Wang and Guo, 2020; Wang and Wan, 2020; Wang and Jiang, 2021; Wu et al., 2002; Yan and Wang, 2003; Xiao and Huang, 2004; Xiao, 2006; Xu and Li, 2006; Xu et al., 2007; Xu and Wang, 2007; Yan and Li, 2008; Xun and Bai, 2010; Xu TWS. et al., 2011; Xu TSWQ. et al., 2011; Xie and Li, 2011; Wu et al., 2012; Xu and Li, 2012; Xu and Yang, 2014; Yan and Bo, 2014; Wu and Wan, 2015; Xu and Wang, 2015; Wu and Tian, 2018; Xu and Wu, 2019; Zhang and Tian, 2008; Yu and Zhao, 2010; Zhan and Wang, 2010; Zhang and Gu, 2010; Yang, 2012; Yu and Wang, 2012; Zhang and Tian, 2012; Ye and Xia, 2014; Yang and Rui, 2015; Zhang and Li, 2015; Zhang and Zhang, 2016; Yu and Zhang, 2017; Yin and Zhang, 2018; Yu and Tang, 2018; Zhang and Zhou, 2018; Yin et al., 2019; Zhang and Bai, 2019; Zhang and Gan, 2020; Zhang and Yan, 2020; Zhang and Ji, 2021; Zhou and Wang, 2005; Zhang and Zhang, 2009; Zhou and Geng, 2009; Zhou and Bao, 2010; Zhao and Hu, 2011; Zhao and Wang, 2011; Zhang and Tang, 2012; Zhao and Zhao, 2012; Zhou and Xiao, 2015; Zhao and Zhang, 2021; Du and Cai, 2005; Zhu and Yang, 2005; Dang and Chu, 2009; Liu and Ku, 2012; Zhu and Li, 2014; Guan and Wang, 2017; Liu et al., 2017; Deng and Li, 2019; Shao and Feng, 2019; Gou and Wu, 2023).

Risk-of-bias assessment

We comprehensively conducted a methodological quality assessment on 198 included RCTs. Based on the summary of the risk of bias, 135 studies (68.2%) were assessed as “some concerns”, 28 studies (14.1%) were rated as “low risk bias”, and 35 studies (17.7%) were classified as “high risk bias”. Overall, these factors result in an overall low-to-moderate risk of bias. The bias risk assessment results were presented in Figure 2.

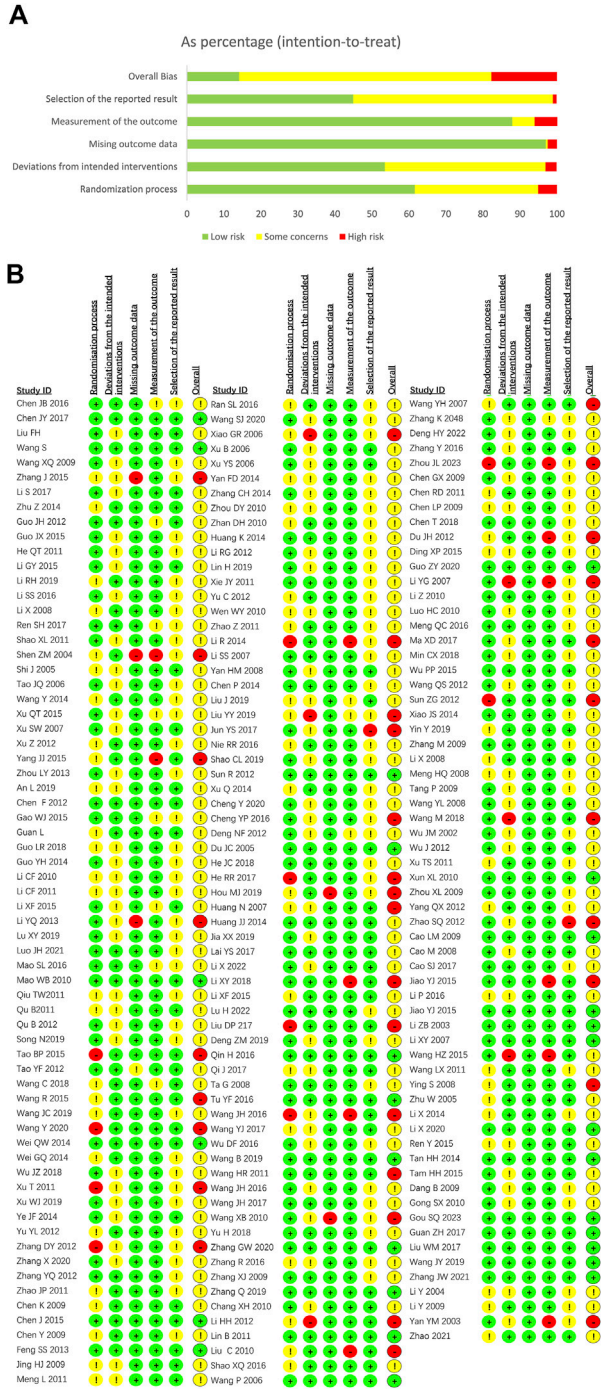

FIGURE 2
Risk assessment results for depression. **(A)** Risk of bias summary for depression; **(B)** Risk of bias graph for depression.

Network diagram

The network diagram provides a visual representation of all the studies included in the meta-analysis and their interconnections. It illustrates how each treatment is compared within the network of studies. The network diagram was outputted to describe the research network graphically. The node size is proportional to the total number of participants in each group. The line width is proportional to the number of clinical trials. When a closed loop is formed between nodes, these studies could be simultaneously compared. Among them, *Fluoxetine*, *Shugan Jieyu Capsule*, and *Chaihu Jia Longgu Muli Decoction* were more extensively studied, followed by *Paroxetine*, *Danzhi-Xiaoyao-San*, and *Jieyu Decoction*. The two groups most frequently compared were *Shugan Jieyu Capsule* and *Fluoxetine*, and *Chaihu Jia Longgu Muli Decotion* and *Fluoxetine*, respectively (Figure 3).

Publication bias and consistency assessment

The nma. fit () function was employed for model fitting and identification of potential outliers. The lever plots and DIC values were utilized to determine the optimal effect model (Watt and Del Giovane, 2022). Figures 4, 5 displayed the lever diagram and consistency test, respectively. Funnel plots presented a symmetrical distribution, thereby indicating limited publication bias (Figure 6).

Trajectory plots (Supplementary Figure S1A) and density plots (Supplementary Figure S1B) were used to assess the degree of convergence. The trajectory plots showed that the MCMC chain stably fluctuates and present good overlap. The density plots indicated excellent model convergence. When the curve tends to 1 and remains stable, it indicates good convergence on the Brooks-Gelman-Rubin diagnostic diagram (Supplementary Figure S2).

Forest map

Forest map focus on these comparisons allows for a direct assessment of how alternative treatments like Chinese herbal medicines stack up against commonly used synthetic antidepressants in terms of both efficacy and safety. Forest maps compare the results of drugs, placebo, or no-treatment in various studies. The treatment efficacy of some Chinese herbal medicines was demonstrated to be generally superior to that of traditional antidepressants. Compared with those in *Fluoxetine*, *Buyang Huanwu Decoction*, *Chai Hu Shu Gan San*, *Chaihu Jia Longgu Muli Decotion*, *Danzhi-Xiaoyao-San*, *Gan Mai Da Zao Decoction*, *Huoxue Soup Decoction*, and *Ease Pill* groups exhibited higher response rates. In addition, interventions of *Buyang Huanwu Decoction* showed a higher response rate compared to *Paroxetine* groups. Moreover, *Amitriptyline* and *Escitalopram* were inferior to *Chaihu Jia Longgu Muli Decoction*. Additionally, *Sertraline* had a lower response rate compared to *Danzhi-Xiaoyao-San* group. Moreover, *Yueju Pill* and *Flupentixol and Melitracen*, *Venlafaxine*, with lower response rates, were comparable to the *Ease Pill* groups. *Jieyu Decoction* was demonstrated to significantly improve depressive symptoms compared to *Venlafaxine* (Figure 7A).

Compared to *Fluoxetine*, patients receiving Chinese herbal medicines, including *Buyang Huanwu Decoction*, *Chai Hu Shu Gan San*, *Chaihu Jia Longgu Muli Decoction*, *Danzhi-Xiaoyao-San*, *Huoxue Soup Decoction*, and *Xiaoyao Powder*, exhibited

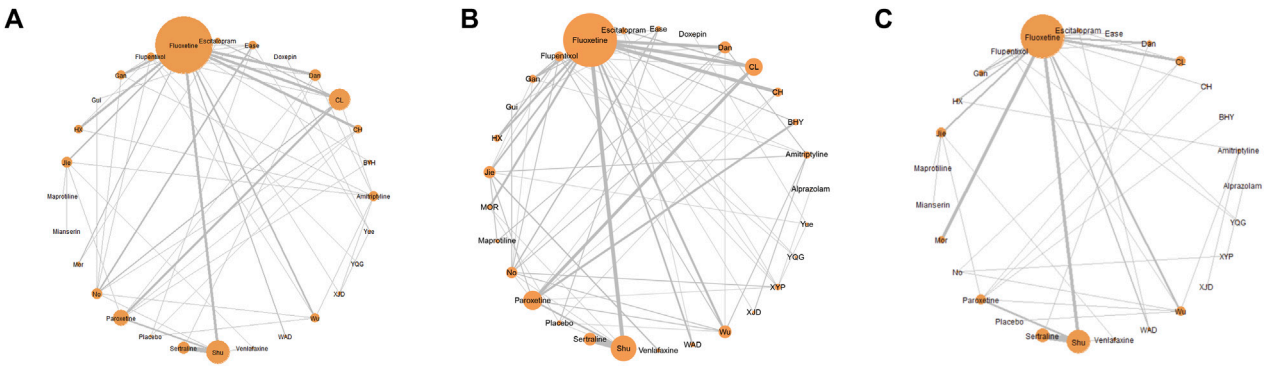

FIGURE 3
Network meta-analysis diagrams of eligible comparisons. **(A)** The response rate; **(B)** HAMD scores; **(C)** adverse effects rate. The size of nodes is proportional to the total number of participants for each group in the network. The edges represent direct comparisons of the drugs in trials. The line width is proportional to the number of trials directly compared at both ends of the nodes. Mor:Morinda Officinalis Oligosaccharide Capsule, Gui: Guipiwan, Jie: Jieyu Decoction, Shu: Shugan Jieyu Capsule, Wu: Wuling Capsule, Ease: Ease Pill, YQG: Yangxue Qingnao Granule, Yue: Yueju Pill, BYH; Buyang Huanwu Decoction, CL: Chaihu Jia Longgu Muli Decoction, CH: Chai Hu Shu Gan San, Dan: Danzhi-Xiaoyao-San, Gan: Gan Mai Da Zao Decoction, HX: Huoxue Soup Decoction, WAD: Wendan Anshen Decoction, XYP: Xiaoyao Powder, XJD: Xingnao Jieyu Decoction.

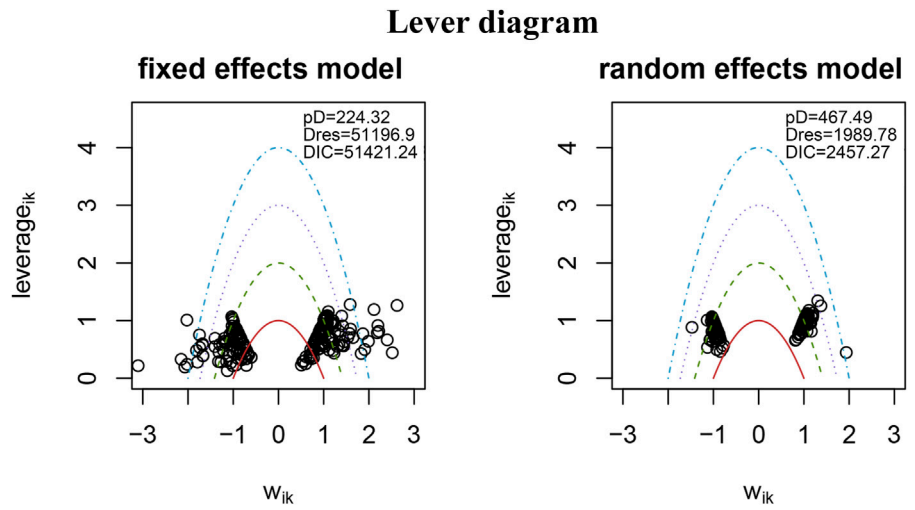

FIGURE 4
Lever diagram for depression. The lever diagram shows the comparison between leverageik and Bayesian deviation residuals of all I tests and each of the K arms.

better efficacy in terms of HAMD scores. In particular, *Chaihu Jia Longgu Muli Decoction* presented a more promising antidepressant effect than *Escitalopram* on HAMD scores (Figure 7B).

In terms of adverse events, *Xingnao Jieyu Decoction* had a significantly lower safety risk than *Amitriptyline*. Compared with *Fluoxetine*, *Chai Hu Shu Gan San*, *Chaihu Jia Longgu Muli Decoction*, *Danzhi-Xiaoyao-San*, *Gan Mai Da Zao Decoction*, *Jieyu Decoction*, *Shugan Jieyu Capsule*, and *Yangxue Qingnao Granule* exhibited lower safety risks of adverse outcomes. Furthermore, compared with *Maprotiline*, *Jieyu Decotion* had lower safety risk. *Jieyu Decoction* had lower safety risk than *Maprotiline*, *Mianserin*, and *Venlafaxine*. *Wuling Capsule* had lower safety risk than *Fluoxetine*, *Flupentixol and Melitracen*, *Paroxetine* (Figure 7C).

The heatmap of the ranking table

The results are presented in a heatmap format, with colors representing the magnitude of effect or ranking probability. The rows of the heatmap typically represent different treatments, while columns represent different outcome measures. Each cell in the heatmap corresponds to the intersection of the categories on the *x* and *y*-axes. The colors in a heatmap are often used to represent a gradient in continuous data. Deep red may indicate higher values, * represents statistically significant data ($p < 0.05$). For instance, in the diagram where the horizontal axis represents *Chai Hu Shu Gan San* and the vertical axis represents *Paroxetine* (**3.11***), there is a statistically significant improvement in the HAMD score for *Chai Hu Shu Gan San* compared to *Paroxetine* ($p < 0.05$).

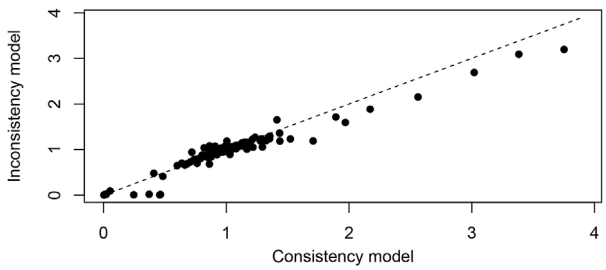

FIGURE 5
Conformance test for depression. The conformance test compares the posterior mean deviation of each data group between consistency and the ume m (b) Bias risk evaluation results displayed by including studies to judge the consistency among the included research results.

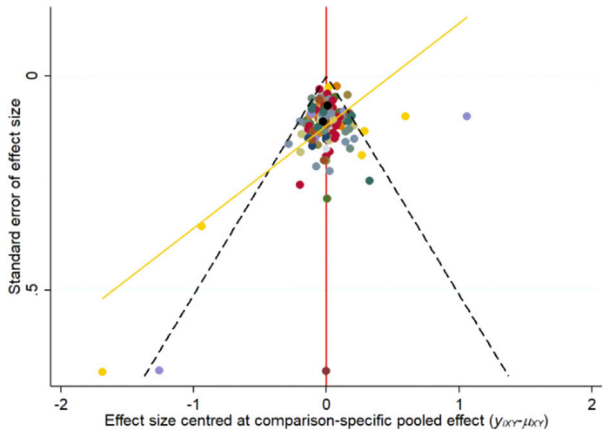

FIGURE 6
Funnel plots. The publication biases were evaluated using funnel plots.

The heatmap of each outcome index ranking table included the 95% *CI* and *OR* of each outcome index across all groups. Interventions involving *Buyang Huanwu Decoction*, *Chai Hu Shu Gan San*, *Chaihu Jia Longgu Muli Decoction*, *Danzhi-Xiaoyao-San*, and *Ease Pill* presented more encouraging point estimates than *Escitalopram*, *Fluoxetine*, *Flupentixol and Melitracen*, *Jieyu Decoction*, *Morinda Officinalis Oligosaccharide Capsule*, *Paroxetine*, *Sertraline*, *Venlafaxine*, and *Shugan Jieyu Capsule*. Moreover, *Gan Mai Da Zao Decoction* and *Guipiwan* were statistically superior in evaluations compared to *Jieyu Decoction*, *Morinda Officinalis Oligosaccharide Capsule*, *Paroxetine*, *Sertraline*, *Venlafaxine*, and *Shugan Jieyu Capsule* (Figure 8A).

Chai Hu Shu Gan San, *Huoxue Soup Decoction* displayed significant effectiveness as active drugs with statistical certainty compared with *Shugan Jieyu Capsule*, *Morinda Officinalis Oligosaccharide Capsule*, *Fluoxetine*, *Wuling Capsule*, *Jieyu Decoction*, *Amitriptyline*, *Sertraline*, *Escitalopram*, *Guipiwan*, and *Yueju Pill* in terms of HAMD scores. *Buyang Huanwu Decoction* and *Xingnao Jieyu Decoction* exhibited greater efficacy than *Fluoxetine*, *Wuling Capsule*, *Jieyu Decoction*, *Amitriptyline*, *Sertraline*, *Escitalopram*, *Guipiwan*, and *Yueju Pill* in terms of HAMD scores. The efficacy of *Danzhi-Xiaoyao-San* and *Chaihu Jia Longgu Muli Decoction* was significantly greater than that of *Fluoxetine*, *Wuling Capsule*, *Sertraline*, *Escitalopram*, and *Yueju Pill* when assessed by HAMD scores (Figure 8B).

Regarding safety outcomes, treatments with a lower risk of depression-related adverse effects were *Xingnao Jieyu Decoction* and *Chai Hu Shu Gan San* (Figure 8C).

SUCRA rankings

After preparing the data with the data. prep () function, we utilized the net. plot () function to graphically depict the research network. The net. plot () function is capable of generating a network diagram for the outcome indicators as needed. SUCRA is a numerical representation method, often presents as a percentage, which is used to summarize the comprehensive ranking of each treatment across multiple outcome indicators. This value is derived from the cumulative ranking probabilities of each treatment, that is consistent with the area under the curve. The SUCRA value is higher, the ranking of the treatment in terms of effectiveness, or safety are higher. The ranking table provides a straightforward way to compare the performance of different interventions or treatments, offers quantitative insights that are more digestible than raw statistical data. The ranking table allows for a direct comparison of the effectiveness and safety of these treatments, making it easier to understand which treatments stand out.

Treatments were ranked for the response rate, HAMD score based on SUCRA values, as illustrated in Table 1. The ranking probability histogram and cumulative probability ranking chart intuitively displayed the sorting probability of each group in Figure 8, consistent with the SUCRA rankings (Table 1).

The results of SUCRA showed that *Guipiwan* may be the most efficacious Chinese herbal medicine to alleviate depressive symptoms but had only a small sample size. Meanwhile, the *Guipiwan* curve was higher than that of other treatments. Significantly, the total response rate of most Chinese herbal medicines was approximately superior to that of traditional antidepressants in this study. *Chai Hu Shu Gan San* was ranked best for the decrease in HAMD scores. *Xingnao Jieyu Decoction* was ranked second for reduction in HAMD scores. Moreover, *Xiaoyao Powder* was ranked best for safety in all treatments. *Maprotiline* was ranked worst for adverse effects rate with poor safety. Importantly, the safety of most Chinese herbal medicines was superior to that of traditional antidepressants in this study (Figure 9).

Summary

This study found that specific Chinese herbal medicines, including *Guipiwan*, *Ease Pill*, *Chaihu Jia Longgu Muli decotion*, *Chai Hu Shu Gan San*, *Danzhi-Xiaoyao-San*, *Gan Mai Da Zao Decoction*, *Buyang Huanwu Decoction* and *Xingnao Jieyu Decoction*, were not only more effective than commonly used synthetic drugs (such as *Fluoxetine*, *Escitalopram*, *Amitriptyline*, *Sertraline*, *Flupentixol*, and *Venlafaxine*) but also associated with a substantially lower risk of adverse events. The findings suggest that Chinese herbal medicines could be considered as viable

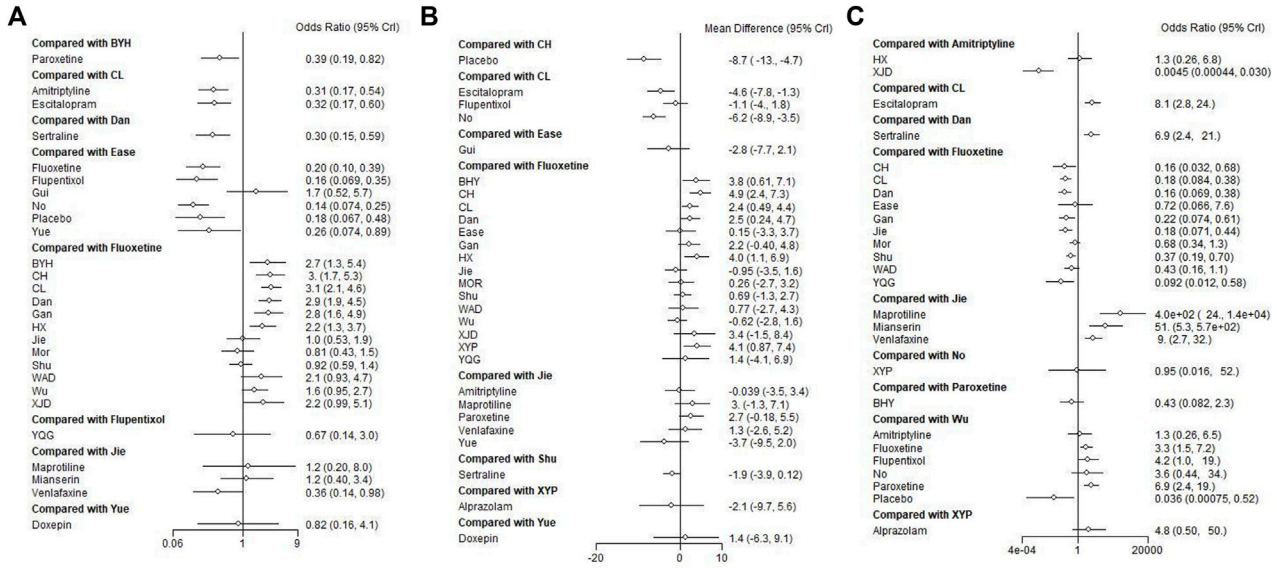

FIGURE 7
Forest plot of the network meta-analysis of all trials for efficacy and adverse effects in patients with depression. **(A)** Direct comparison of the response rate; **(B)** direct comparison of HAMD scores; **(C)** direct comparison of the adverse effects rate. Mor:Morinda Officinalis Oligosaccharide Capsule, Gui: Guipiwan, Jie: Jieyu Decoction, Shu: Shugan Jieyu Capsule, Wu: Wuling Capsule, Ease: Ease Pill, YQG: Yangxue Qingnao Granule, Yue: Yueju Pill, BYH: Buyang Huanwu Decoction, CL: Chaihu Jia Longgu Muli Decoction, CH: Chai Hu Shu Gan San, Dan: Danzhi-Xiaoyao-San, Gan: Gan Mai Da Zao Decoction, HX: Huoxue Soup Decoction, WAD: Wendan Anshen Decoction, XYP: Xiaoyao Powder, XJD: Xingnao Jieyu Decoction.

alternatives to synthetic antidepressants for the treatment of depression, particularly for patients who might be looking for natural remedies or those who are intolerant to the side effects of synthetic drugs. These results could inform clinical practice by expanding the range of treatment options available for depression, potentially leading to more personalized and effective treatment strategies.

Discussion

In summary, this is the first study to systematically evaluate the safety and efficacy of 17 different Chinese herbal medicines attenuating depressive symptoms in depression patients. A Bayesian network meta-analysis was performed to explore the efficacy of single Chinese herbal medicines. The RoB2 was used to assess the methodological quality.

Principal findings

In network diagram, *Fluoxetine*, *Shugan Jieyu Capsule*, and *Chaihu Jia Longgu Muli Decoction* were more extensively studied, followed by *Paroxetine*, *Danzhi-Xiaoyao-San*, and *Jieyu Decoction*. In heatmap, the interventions of *Buyang Huanwu Decoction*, *Chai Hu Shu Gan San*, *Chaihu Jia Longgu Muli Decoction*, *Danzhi-Xiaoyao-San*, and *Ease Pill*, *Gan Mai Da Zao Decoction* and *Guipiwan* presented more encouraging point estimates. Through direct comparison of forest map, the treatment efficacy of some Chinese herbal medicines was shown to be broadly greater than that of traditional antidepressants. According to SUCRA ranking, *Guipiwan* (SUCRA value: 96.93%) had the highest efficacy, closely followed by *Ease Pill* (SUCRA value: 93.76%), *Chaihu Jia Longgu Muli Decoction* (SUCRA value: 83.37%), *Chai Hu Shu Gan San* (SUCRA value: 81.44%), and *Danzhi-Xiaoyao-San* (SUCRA value: 80.61%). Notably, *Xiaoyao Powder* exhibited the lowest incidence of adverse events (SUCRA value: 98.23%). Moreover, commonly used synthetic drugs such as *Amitriptyline* (SUCRA value: 51.57%), *Fluoxetine* (SUCRA value: 28.48%), *Venlafaxine* (SUCRA value: 28.12%), *Escitalopram* (SUCRA value: 23.39%), *Sertraline* (SUCRA value: 26.98%), *Flupentixol* (SUCRA value: 8.51%) and *Maprotiline* (SUCRA value: 0.03%), appeared to be less effective and carried higher risks of adverse events compared to most Chinese herbal medicines. Moreover, commonly used synthetic drugs such as *Fluoxetine*, *Escitalopram*, *Amitriptyline*, *Sertraline*, *Flupentixol and Melitracen*, and *Venlafaxine*, appeared to be less effective and carried higher risks of adverse events compared to most Chinese herbal medicines.

The mechanism of Chinese herbal medicines on depression

After thousands of years of exploration, Chinese herbal medicine has been shown advantages in the treatment of depression, such as multiple components, multitarget and strong safety, which plays a critical role in treating depression (Yeung et al., 2014b; Wang et al., 2017). The mechanisms of Chinese herbal medicines on treatment of depression are still largely unknown. The underlying pathophysiology of depression is associated with the damage of monoamine transmission systems (LeMoult and Gotlib,

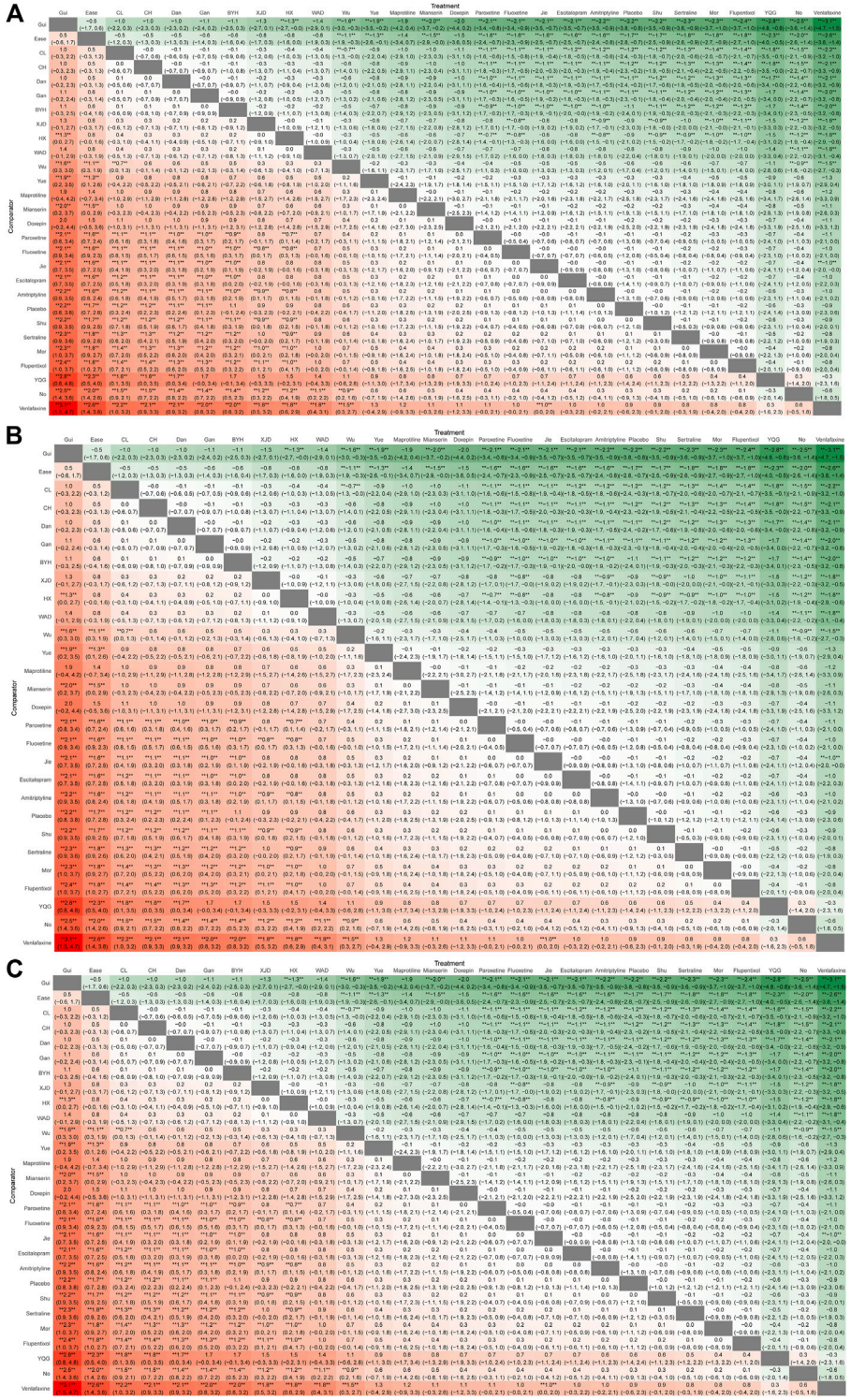

FIGURE 8
Ranking chart heatmap for depression. The heatmap of each outcome index ranking table shows comparisons of the relative effects between any pair of interventions, including the OR and 95% CI of each outcome index in all groups. **(A)** The response rate ranking chart heatmap; **(B)** HAMD scores ranking chart heatmap; **(C)** adverse effects rate ranking chart heatmap. Mor:Morinda Officinalis Oligosaccharide Capsule, Gui: Guipiwan, Jie: Jieyu Decoction, Shu: Shugan Jieyu Capsule, Wu: Wuling Capsule, Ease: Ease Pill, YQG: Yangxue Qingnao Granule, Yue: Yueju Pill, BYH: Buyang Huanwu Decoction, CL: Chaihu Jia Longgu Muli Decoction, CH: Chai Hu Shu Gan San, Dan: Danzhi-Xiaoyao-San, Gan: Gan Mai Da Zao Decoction, HX: Huoxue Soup Decoction, WAD: Wendan Anshen Decoction, XYP: Xiaoyao Powder, XJD: Xingnao Jieyu Decoction.

TABLE 1 SUCRA rankings.

Efficacy				Safety	
The effective rate	SUCRA(%)	HAMD	SUCRA(%)	Adverse effects rate	SUCRA(%)
Gui	96.93	CH	89.96	XYP	98.23
Ease	93.76	XJD	87.40	Alprazolam	95.25
CL	83.37	XYP	84.19	XJD	91.98
CH	81.44	BHY	82.50	Placebo	91.41
Dan	80.61	HX	77.36	CH	78.51
Gan	78.58	Dan	76.00	YQG	74.75
BYH	76.71	Maprotiline	73.28	Jie	73.09
XJD	70.93	CL	68.41	CL	70.46
HX	70.55	Paroxetine	63.52	Gan	66.82
WAD	67.73	Venlafaxine	60.74	Dan	63.45
Wu	58.02	Amitriptyline	60.35	Wu	61.63
Yue	46.60	Alprazolam	59.93	Shu	53.39
Maprotiline	46.25	Jie	50.90	Amitriptyline	51.57
Mianserin	43.20	Shu	49.94	WAD	47.84
Doxepin	40.87	WAD	48.34	HX	41.46
Paroxetine	38.31	YQG	46.65	BHY	38.64
Fluoxetine	36.63	MOR	45.28	Mor	38.05
Jie	36.12	Easa	44.70	Ease	37.47
Escitalopram	35.81	Gan	43.70	Fluoxetine	28.48
Amitriptyline	33.79	Fluoxetine	39.13	Venlafaxine	28.12
Placebo	31.62	Wu	34.76	No	27.57
Shu	31.62	Flupentixol	33.32	Sertraline	26.98
Sertraline	27.86	Doxepin	31.12	Escitalopram	23.39
Mor	25.56	Sertraline	28.63	Paroxetine	20.85
Flupentixol	25.22	Gui	16.62	Mianserin	12.06
YQG	19.38	Escitalopram	16.18	Flupentixol	8.51
No	16.59	Yue	15.63	Maprotiline	0.03
Venlafaxine	5.95	Placebo	11.76		
		No	9.70		

SUCRA, surface under the cumulative ranking; Mor, Morinda Officinalis Oligosaccharide Capsule; Gui, Guipiwan; Jie, Jieyu Decoction; Shu, Shugan Jieyu Capsule; Wu, Wuling Capsule; Ease, Ease Pill; YQG, yangxue qingnao granule; Yue, Yueju Pill; BYH, buyang huanwu decoction; CL, chaihu jia longgu muli decoction; CH, chai hu shu gan san; Dan, Danzhi-Xiaoyao-San; Gan, Gan Mai Da Zao Decoction; HX, huoxue soup decoction; WAD, wendan anshen decoction; XYP, xiaoyao powder; XJD, xingnao jieyu decoction.

2019). In fact, clinical studies have found that *Chaihu Jia Longgu Muli Decoction*, *Gan Mai Da Zao Decoction*, *Xiao Yao San* has a good antidepressant effect by preventing dopaminergic transmission in rats (Ding et al., 2021; Wan et al., 2021; Wang YT. et al., 2023). This core active ingredients of *Chaihu Jia Longgu Muli Decoction* consists of *Chaihu (Bupleurum)*, *Muli (Ostrea gigas)*, which are pivotal in treating depression (Wang Y. et al., 2023). The key active compounds in the *Gan Mai Da Zao Decoction* were identified as *Quercetin*, *Luteolin*, *Kaempferol*, *Naringenin*, and *Isorhamnetin*, contributing significantly to its antidepressant effect (Ding et al., 2021). *Quercetin*, *Apigeni* and *Luteolin*, key components of the *Xiao Yao San*, effectively mitigate the progression of depression (Chen, 2023).

Inflammation and mitochondrial dysfunction are also associated with the pathogenesis of depression (Bansal and Kuhad, 2016; Kohler et al., 2016). In addition, *Morinda Officinalis Oligosaccharide Capsule* mitigate depression by regulating Mitofusin two protein-mediated mitophagy in rats (Yang et al., 2023). *Morinda Officinalis Oligosaccharide Capsule* mainly contains

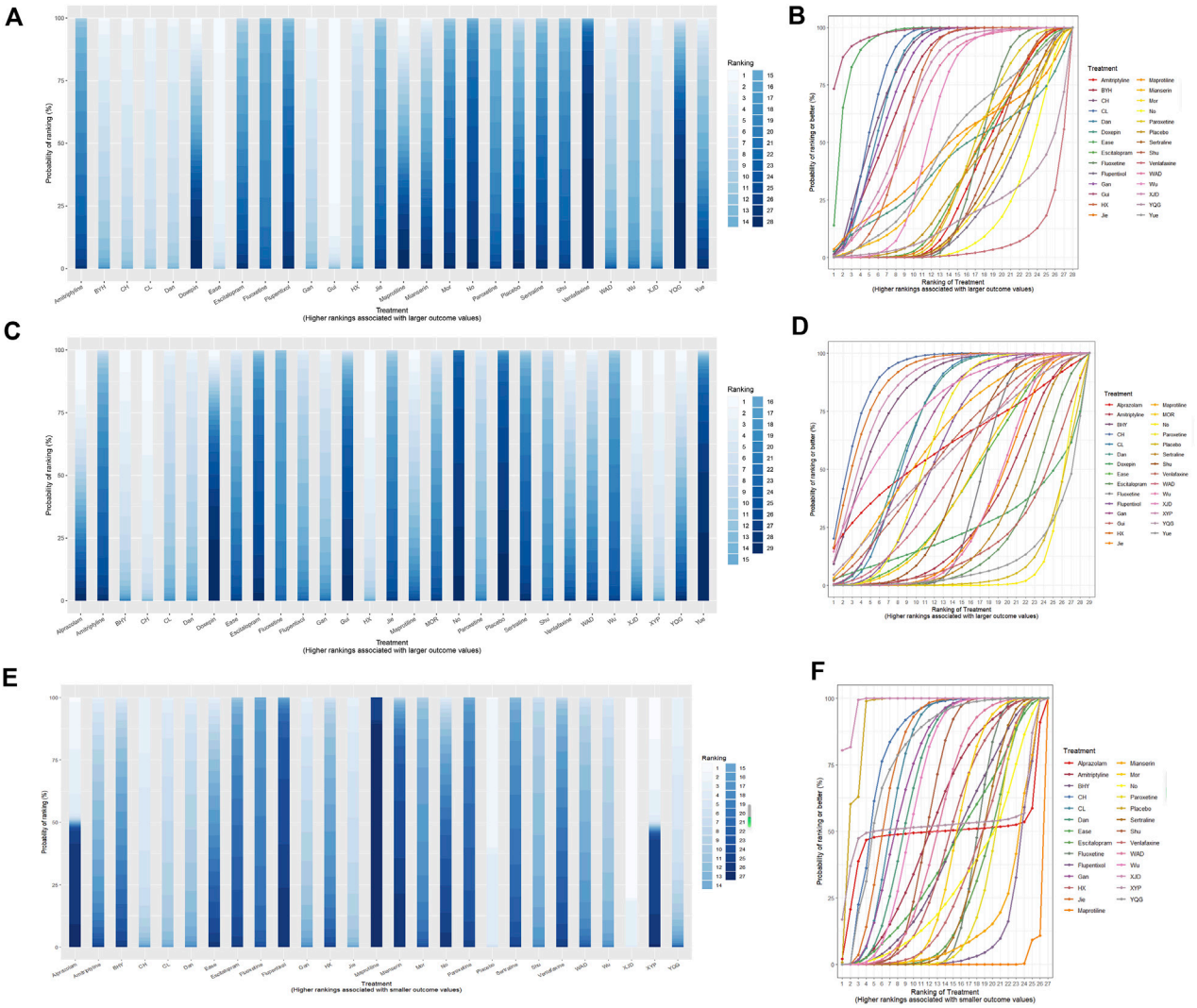

FIGURE 9
Ranking probability histogram and cumulative probability ranking chart for depression. The histogram and SUCRA charts intuitively display the sorting probability of each group in the form of histograms and curves. **(A)** Rankogram chart of response rate; **(B)** SUCRA chart of the response rate; **(C)** rankogram chart of HAMD scores; **(D)** SUCRA chart of HAMD scores; **(E)** rankogram chart of adverse effects rate; **(F)** SUCRA chart of adverse effects rate. Mor:Morinda Officinalis Oligosaccharide Capsule, Gui: Guipiwan, Jie: Jieyu Decoction, Shu: Shugan Jieyu Capsule, Wu: Wuling Capsule, Ease: Ease Pill, YQG: Yangxue Qingnao Granule, Yue: Yueju Pill, BYH: Buyang Huanwu Decoction, CL: Chaihu Jia Longgu Muli Decoction, CH: Chai Hu Shu Gan San, Dan: Danzhi-Xiaoyao-San, Gan: Gan Mai Da Zao Decoction, HX: Huoxue Soup Decoction, WAD: Wendan Anshen Decoction, XYP: Xiaoyao Powder, XJD: Xingnao Jieyu Decoction.

inulin-type oligosaccharides extracted from the roots of M. officinalis, which is effective in ameliorating symptoms of depressive disorder (Zhang et al., 2018). Furthermore, *Wuling Capsule* mitigate depression by regulating translocator protein-mediated mitophagy, exhibit antioxidant and anti-inflammatory effects in rats (Zheng et al., 2016). *Wuling Capsule* is mainly formulated with *Wulingshen powder*, which is a kind of fungal sclerotia of a ginseng. *Wulingshen* contains flavonoids, triterpenoids, saponins and polysaccharides, which are beneficial in improving depression (Feng et al., 2016). *Chai Hu Shu Gan San* is composed of *Chaihu (Bupleuri radix)*, *Xiangfu (Cyperus rhizome)*, and *Chuanxiong (Ligusticum chuanxiong rhizome)*, which have anti-inflammatory actions and neuroprotective effects (Sun et al., 2018).

Expectation and actual findings

The expectation of this study was Chinese herbal medicines exhibit better efficacy, and fewer side effects compared with synthetic antidepressants for the treatment of depression. It was expected to provide insights into the potential of Traditional Chinese Medicines as promising alternatives to conventional antidepressants.

The actual findings from this study are significant as they suggest that Chinese herbal medicines might be viable alternative therapies for depression, potentially offering benefits in terms of effectiveness and safety. In terms of clinical practice, these findings can inform healthcare professionals about alternative treatment options, especially for patients who may seek or prefer herbal remedies or for whom traditional antidepressants are not suitable. However, the generalizability of these

results may be influenced by the study's methodology and the specific patient populations included in the analyzed trials. Further research is needed to explore these findings in varied clinical settings and among diverse patient populations to fully ascertain the generalizability and practical application of the study's conclusions.

Potential confounding factors or biases

The variation in risk of bias across different studies may impact outcomes, potentially affecting the reliability of comparisons between Chinese herbal medicines and synthetic drugs. Chinese herbal medicines and synthetic drugs often differ in their mechanisms of action, side effects, and patient adherence rates. These differences could introduce confounding factors in comparative analyses. The acceptance and use of Chinese herbal medicines might be influenced by cultural beliefs and practices, which could affect patient outcomes. Geographic locations of these studies could also introduce biases, as herbal medicine practices may vary significantly across regions. Specific characteristics of patient populations in the studies, such as severity of depression, age, gender, and comorbidities, can influence the effectiveness and safety of the treatments.

Strengths and limitations

We performed a comprehensive literature search focused on depression, addressed crucial outcomes, and rigorously assessed risk of bias at the level of evidence. The acceptability of various interventions was assessed based on criteria such as response rate, HAMD scores, and rate of adverse events on *versus* direct and indirect comparisons, thereby enhancing the persuasiveness of the evidence.

Traditional Chinese medicines are emerging as promising new drug candidates for depression treatment (Huhn, et al., 2020). This study aims to aims to determine the effectiveness, acceptability, and safety of Chinese herbal medicines in comparison with synthetic antidepressants. In addition, this study provides reference information suggesting that Chinese herbal medicines could serve as viable alternative therapies as natural remedies.

However, there are some limitations in this study. HAMD scores were used as the efficacy outcomes. Nevertheless, the data from other depression scales, such as Self-rating Depression Scale scores and Hamilton Anxiety Scale scores, were excluded due to a lack of sufficient clinical trials. These findings may lead to more complete conclusions about Chinese herbal medicines on depression. Remarkably, this study did not compare the multiple Chinese herbal medicine treatments according to the severity of depression. This review included numerous studies with small sample sizes, which limited the certainty of current evidence for the clinical use of Chinese medicines (Bian et al., 2020). Therefore, larger, more rigorous trials are necessary in the future.

Conclusion

The study is the first to systematically assess the efficacy and safety of traditional Chinese medicines for treating depression patients using Bayesian network meta-analysis. We conclude that *Guipiwan*, *Ease Pill*, *Chaihu Jia Longgu Muli Decoction*, *Chai Hu Shu Gan San*, *Danzhi-Xiaoyao-San*, *Buyang Huanwu Decoction*, *Xiaoyao Powder*, *Huoxue Soup Decoction*, *Wendan Anshen Decoction*, *Wuling Capsule*, and *Yueju Pill* have great promise for treating depression. Further research is necessary in larger sample sizes, diverse patient populations, long-term efficacy and safety investigations comparing multiple Chinese herbal medicine treatments based on depression severity.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Author contributions

CD: Writing–original draft, Investigation. QW: Data curation, Software, Writing–original draft, Methodology. QL: Funding acquisition, Writing–review and editing, Investigation. YX: Writing–review and editing, Methodology. YL: Data curation, Investigation, Writing–original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1295564/full#supplementary-material

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