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Review paper

Luteolin and its antidepressant properties: From mechanism of action to potential therapeutic application

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ABSTRACT

Luteolin is a natural flavonoid compound exists in various fruits and vegetables. Recent studies have indicated that luteolin has variety pharmacological effects, including a wide range of antidepressant properties. Here, we systematically review the preclinical studies and limited clinical evidence on the antidepressant and neuroprotective effects of luteolin to fully explore its antidepressant power. Network pharmacology and molecular docking analyses contribute to a better understanding of the preclinical models of depression and antidepressant properties of luteolin. Seventeen preclinical studies were included that combined network pharmacology and molecular docking analyses to clarify the antidepressant mechanism of luteolin and its antidepressant targets. The antidepressant effects of luteolin may involve promoting intracellular noradrenaline (NE) uptake; inhibiting 5-hydroxytryptamine (5-HT) reuptake; upregulating the expression of synaptophysin, postsynaptic density protein 95, brain-derived neurotrophic factor, B cell lymphoma protein-2, superoxide dismutase, and glutathione *S*-transferase; and decreasing the expression of malondialdehyde, caspase-3, and amyloid-beta peptides. The antidepressant effects of luteolin are mediated by various mechanisms, including anti-oxidative stress, anti-apoptosis, anti-inflammation, anti-endoplasmic reticulum stress, dopamine transport, synaptic protection, hypothalamic–pituitary–adrenal axis regulation, and 5-HT metabolism. Additionally, we identified insulin-like growth factor 1 receptor (IGF1R), AKT serine/threonine kinase 1 (AKT1), prostaglandin-endoperoxide synthase 2 (PTGS2), estrogen receptor alpha (ESR1), and epidermal growth factor receptor (EGFR) as potential targets, luteolin has an ideal affinity for these targets, suggesting that it may play a positive role in depression through multiple targets, mechanisms, and pathways. However, the clinical efficacy of luteolin and its potential direct targets must be confirmed in further multicenter clinical case-control and molecular targeting studies.

1. Introduction

Depression is a common disorder that endangers mental health and reduces the quality of daily life. It is also the third-highest contributor to the global burden and is likely to become the first by 2030 [1]. The global annual incidence of depression is approximately 6%, with no statistically significant difference between high-income developed countries (5.5%) and low-income developing countries (5.9%) [2], and approximately one in five people experience a depressive episode at some point in their lifetime [3]. Middle-aged people around the age of 45 years comprise the main population of people with depression, and appropriately 40% experienced their first depressive episode before the age of 20 [4], with the second and third peaks occurring at 50 and 60 years of age, respectively. The incidence was significantly higher in women than in men [5].

With the rapid pace of modern life, continuous tension and stress have become causes of depression. A stress response is a highly conservative behavior that can improve survival in uncontrollable and unpredictable environmental changes; however, excessive stress can cause physical damage [6]. Stress can act on the body's neuroendocrine system by affecting brain structure, neurotransmitter regulation, excitotoxicity, metabolic disorders, and other pathways and is involved in the pathogenesis of depression [7]. Several hypotheses have been proposed for the pathogenesis of depression. First, depression may arise from structural brain abnormalities: The orbitofrontal cortex (OFC) is a part of the prefrontal cortex, which has direct or indirect neural connections with brain areas including the hippocampus,

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amygdala, hypothalamus, and caudate nucleus. It is regulated by interneuron circuits, coordinates a range of activities in the central nervous system (CNS), and plays a key role in emotional processing, reward encoding, and goal-directed learning. Early stress experience is not only related to structural changes in the OFC area but also increases depression risk [8]. Second, the hypothalamic–pituitary axis (HPA) is overactive in patients with depression, which may be caused by a disturbance in the negative feedback loop of glucocorticoid receptors on the HPA axis. Cortisol levels may determine the risk and timing of depressive episodes in patients with depression, suggesting that HPA axis dysfunction is associated with the pathogenesis of depression [9]. Third, the inflammatory hypothesis reflects that proinflammatory cytokines interleukin and acute phase C-reactive protein levels are significantly increased in patients with depression [10]. Thus, the upregulation of inflammation may be involved in the occurrence and development of depression by decreasing monoamine neurotransmitters, such as serotonin, and increasing tryptophan metabolites, which have toxic effects on the brain [11]. Fourth, concerning the vitamin D hypothesis, vitamin D is mainly synthesized by the body itself, and plasma vitamin D levels are decreased in patients with depression accompanied by cognitive impairment, suggesting that vitamin D may be involved in the pathogenesis of depression [12].

The initial treatment plans for depression include psychotherapy, drug treatment, or combined treatment [13]. For patients with mild depression, evidence-based medicine suggests that psychotherapy, such as cognitive behavioral therapy, should be administered as the first-line treatment [14]. Psychotherapy can also be used alone in patients with moderate disease; however, the combined treatment effect is more significant. For patients with severe depression, drug therapy should be used as the first-line treatment option. This commonly includes selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and noradrenergic and specific serotonergic antidepressants [15]. And noradrenaline-dopamine reuptake inhibitors and electroconvulsive therapy can be considered when patients do not respond well to medication [16]. However, even after regular long-term treatment, patients with depression will experience recurrent episodes that are difficult to treat. The highly variable clinical presentation of depression, difficulty in estimating its course and prognosis, and slow response and side effects of antidepressant treatment (e.g., nausea, headaches, liver injury, and cardiovascular disease risk) have prompted the search for novel, multitargeted, safe, and effective antidepressants [17].

Luteolin (3, 4, 5, 7-tetrahydroxyflavone), the structure of which is shown in Fig. 1, is a natural flavonoid originally obtained from *Reseda odorata* L. of the Luteolin family [18]. It can be seen from the structure that luteolin is a polyphenolic hydroxyl compound with poor lipophilicity. Owing to the intermolecular force between the hydroxyl groups, the lattice energy is high and its hydrophilicity is also poor [19]. Luteolin has a rich pharmacological effect and strong medicinal value. Luteolin can reduce the occurrence of neuropathy, protect the nervous system, and improve memory and cognitive function [20]. In addition, luteolin can inhibit tumor cell proliferation and promote apoptosis to exert an anti-tumor effect [21]. Luteolin is derived from a wide range of sources and present in various herbs. For example, *Dracocephalum integrifolium*, *Lonicera japonica* Thunb., *Scutellaria baicalensis Georgi*, *Scutellaria barbata* D., and *Chrysanthemum indicum* L. have been suggested to have antidepressant effects in several preclinical studies [22]. We summarize the antidepressant effects, pharmacokinetics, medicinal value, and toxicity of luteolin by combining the results of *in vitro* and *in vivo* studies. In addition, we use network pharmacology analysis to investigate the potential antidepressant mechanisms of luteolin, which are further verified by molecular docking. Luteolin may exert its antidepressant effects through multiple mechanisms and has the potential to become a new antidepressant.

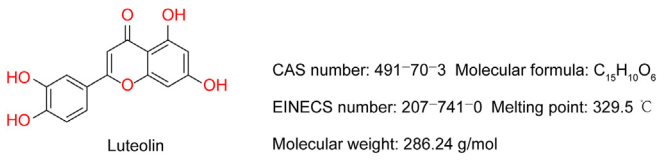

Fig. 1. Common sources and chemical structures of luteolin. CAS: Chemical Abstracts Service; EINECS: European Inventory of Existing Commercial Chemical Substances.

2. Antidepressant studies of luteolin

2.1. Search strategy

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, relevant studies published up to December 2023 were extracted from the Web of Science, PubMed, ScienceDirect, and Google Scholar (Fig. 2). The following search terms were used for each database: 1) luteolin; 2) 3,4,5,7-tetrahydroxy flavone; 3) lut; 4) or/(1)–(3); 5) depression; 6) depressive symptoms; 7) emotional depressions; 8) neuroprotection; 9) or/5)–8); and 10) 4) and 9).

2.2. Inclusion and exclusion criteria

We included *in vitro* and *in vivo* studies on luteolin treatment in depression models. These studies analyzed the effect of luteolin on depression models, its potential therapeutic effect on depression, and its mechanism through *in vivo* behavioral studies and *in vitro* pathological experiments. The inclusion criteria for this systematic review were as follows: 1) both *in vitro* and *in vivo* models should be treated with luteolin; 2) the studies must include a control group; 3) the content of the studies must be relevant to depression; and 4) studies must be published in English. The exclusion criteria were as follows: 1) review articles, 2) duplicate articles, and 3) studies on luteolin in combination with other herbs.

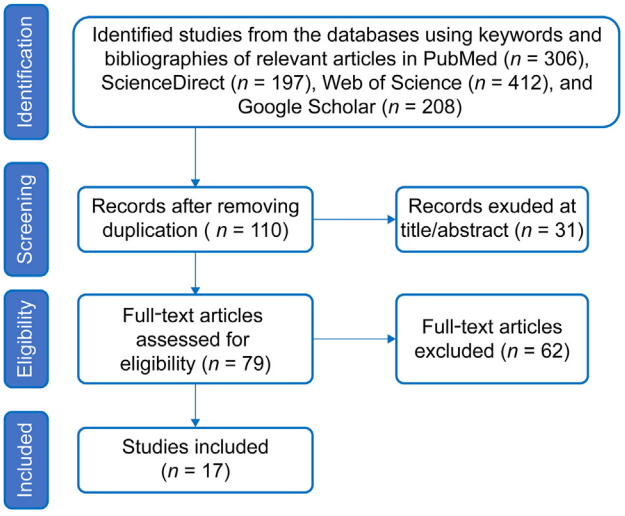

Fig. 2. Process used to select appropriate articles using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.3. Literature screening and data extraction

Original articles were collected independently by two authors according to the inclusion and exclusion criteria, and disputes were resolved through discussion.

2.4. Target prediction of luteolin action

Two methods are used to predict potential targets of luteolin: 1) PharmMapper: use ChemBioDraw 12.0 software to draw the chemical structure of luteolin and save it in "Mol2" format. The reverse pharmacophore matching method was used to upload it to the forecast targets PharmMapper server (https://www.lilab-ecust.cn/pharmmapper/submitfile.html). The parameters were set as: generate conformers: Yes; maximum generated conformations: 100; select target set: human protein target only [23]. 2) SwissTargetPrediction (https://swisstargetprediction.ch/) database: "Luteolin" as keywords to search [24]. Targets with PharmMapper prediction and matching scores and those obtained from the SwissTargetPrediction database were searched using the UniProt database (https://www.uniprot.org/), with the species defined as human and the names of the targets normalized.

2.5. Depression-related target retrieval

Using the keyword "depression", we utilized the Online Mendelian Inheritance in Man database (OMIM, https://www.omim.org/), Therapeutic Target Database (https://db.idrblab.org/ttd/), Disease Gene Search Engine database (DigSee, http://210.107.182.61/genesearch/), and Comparative Toxicology Database (CTD, http://ctdbase.org/) to retrieve and filter, remove duplicate targets, obtain targets related to depression, and standardize targets using the UniProt database.

2.6. Functional annotation and pathway enrichment analysis of target genes

By comparing and analyzing the obtained targets of luteolin with those related to depression, we identified potential targets for luteolin-based depression treatment. We imported the obtained targets into the Database for Annotation Visualization and Integrated Discovery (DAVID, https://david.ncifcrf.gov/) and performed Gene Ontology (GO) enrichment and Kyoto Encyclopedia of Genes and Genome (KEGG) pathway annotation analyses on the targets.

2.7. Component-target-pathway interaction network construction

We used Cytoscape 3.9.1 software to construct the interaction network between luteolin targets for depression treatment and the KEGG pathway. The network included two types of nodes (target and action pathways), and the target protein and its corresponding action pathway were connected by an edge. The Network Analyzer plug-in, which refers to the number of connections a node has, was used to calculate node degree. The higher the node degree, the more critical the node. The key target proteins and pathways of luteolin in depression treatment were obtained through analysis.

2.8. Molecular docking

We downloaded the three-dimensional structure of luteolin from the PubChem website (https://www.PubChem.ncbi,nlm.nih.gov) and docking targets with higher degrees to luteolin. We used PyMol software to edit the structure of the key target and AutoDock software to set luteolin as a semi-flexible docking ligand with the key target, perform molecular docking, evaluate the interaction and binding mode, and display the lowest binding energy. The lower the binding energy, the stronger the interaction between them, and the more stable the molecular conformation. Finally, the results were visualized using PyMol and Maestro software.

3. Antidepressant effects of traditional Chinese medicine (TCM) preparations containing luteolin

Research increasingly shows that Chinese herbal medicine and TCM preparations containing luteolin exert antidepressant and neuroprotective effects through various mechanisms, thus indirectly suggesting the antidepressant potential of luteolin.

3.1. Chinese herbal medicine

Luteolin is a main pharmacological component of ethanol extracted from peanut shells (PSE) [25]. In the chronic unpredictable mild stress (CUMS)-induced depression rat model, gavage of PSE (100−900 mg/kg/day) significantly improved depressive behavior. The antidepressant mechanism of PSE was further investigated. The results showed that PSE increased the levels of 5-hydroxytryptamine (5-HT), noradrenaline (NE), dopamine (DA), and neurotrophic factors, and decreased the levels of adrenocorticotropic hormone (ACTH) and corticotropin-releasing factors. PSE can inhibit the release of inflammatory factors interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α), and regulate intestinal flora, suggesting that PSE may exert an antidepressant effect through multiple mechanisms [26].

Ethanol extract of *Clerodendrum serratum* (EECS) Linn. primarily contained luteolin and flavonoid components. Evaluations of the effects of the EECS on depression-like behavioral symptoms in adult mice showed that EECS had therapeutic effects on depressive behavior through anti-oxidative stress (OS) and neurotransmitter regulation. For example, EECS was found to significantly increase the activity of the antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT), inhibit the activity and content of glutathione peroxidase (GPX) and malondialdehyde (MDA), and promote the levels of neurotransmitters such as NE and 5-HT [27].

Previous studies have shown that *Rosmarinus officinalis* and its active compounds, luteolin and betulinic acid, exhibit neuroprotective effects *in vitro* and *in vivo*, which may be related to improved cholinergic effects and mitogen-activated protein kinase/extracellular signal-regulated kinase 1 and 2 (MAPK/ERK1/2) signaling pathway [28]. Sasaki et al. [29] further validated the antidepressant mechanism of *Rosmarinus officinalis* using both *in vivo* and *in vitro* experiments. Proteomic analysis showed that *Rosmarinus officinalis* significantly upregulated the levels of tyrosine hydroxylase (TH) and pyruvate carboxylase (PC), two major genes involved in the regulation of the DA, 5-HT, and γ-aminobutyric acid-ergic (GABAergic) pathways. Additionally, *Rosmarinus officinalis* protected neuronal cells from corticosteroid-induced toxicity and increased the levels of several neurotransmitters (DA, NE, 5-HT, and acetylcholine (ACH)) in the brain. This study contributed to the understanding of the antidepressant effects of *Rosmarinus officinalis* and its major active compounds.

Eremostachys laciniata is a rich source of flavonoids and luteolin is one major active compounds isolated from it. Nisar et al. [30] investigated the chemical composition and *in vivo* antidepressant effects using the forced swimming test (FST) model and suggested that *Eremostachys laciniata* extract has a significant antidepressant effect at low doses, whereas increased immobility time was observed at higher doses. This may be because of the pharmacological and calming effects of luteolin, and *Eremostachys laciniata* may be a source for the isolation of important natural products with antidepressant properties.

3.2. TCM preparations

TCM prescriptions are still the main way for TCM to exert its therapeutic effects on diseases, although the pharmacological mechanism of TCM prescriptions has faced some controversy. Research into TCM preparations for the treatment of depression is currently in progress. Danzhi-Xiaoyao-San (DZXYS) has been reported to exert an essential effect in the clinical treatment of depression. In a double-blind randomized controlled clinical trial, the combination of DZXYS and SSRIs improved depressive symptoms more than SSRIs alone. The pharmacological mechanism of DZXYS was investigated and the results suggested that quercetin and luteolin were the main active components of DZXYS. Molecular docking revealed that arginine vasopressin receptor 2 (*AVPR2*), cyclin-dependent kinase 6 (*CDK6*), epidermal growth factor receptor (*EGFR*), and coagulation factor II (*F2*), and their enriched pathways, were the main targets of luteolin. Its regulatory effect on gut microbiota is another major antidepressant mechanism of DZXYS [31]. Zhi-Zi-Hou-Po Decoction (ZZHPD) is also used clinically to treat depression. By establishing a novel liquid chromatography-mass spectrometry method, Feng et al. [32] further investigated the active components of ZZHPD, and the results suggested that luteolin, as an active plant component that can be absorbed into brain tissue, played a key role in the antidepressant effect of ZZHPD. Molecular modeling further suggested that glyoxalase 1 (*GLO1*), monoamine oxidase B (*MAOB*), melatonin receptor 1A (*MTNR1A*), and solute carrier family 6 member 4 (*SLC6A4*) are potential targets of luteolin, which may further shed light on the antidepressant effects of ZZHPD. Chaihu Shugan San (CSS) has been used in clinical and preclinical depression treatment with good safety and efficacy. However, the active components of CSS and their antidepressant mechanisms remain unclear. In a mouse model induced by CUMS, Zhang et al. [33] investigated the antidepressant mechanism of CSS and found that CSS treatment significantly reversed CUMS-induced alterations in phosphorylated phosphoinositide 3-kinase (PI3K) and phosphorylated protein kinase B (AKT) expression, while decreasing glycogen synthase kinase-3beta (GSK3β) expression, suggesting that the PI3K/AKT/GSK3β pathway may be involved in the antidepressant effects of CSS. Luteolin and quercetin are the main active ingredients in CSS. Molecular simulation studies further confirmed that PI3K is the main target of the two active ingredients, providing theoretical support for further understanding the antidepressant mechanism of CSS.

Network pharmacology has been widely used to explore the pharmacological mechanisms and drug targets of TCM prescription [34]. Although Shugan Jieyu Capsule (SJC) has been widely used to treat clinical depression, its antidepressant mechanism remains controversial. Hyperforin, kaempferol, luteolin, and quercetin are the core active ingredients of SJC, Molecular modeling studies further confirmed that *AKT1*, caspase 3 (*CASP3*), *IL6*, *IL1B*, Jun proto-oncogene (*JUN*), *MAPK3*, prostaglandin-endoperoxide synthase 2 (*PTGS2*), *TNF*, and vascular endothelial growth factor A (*VEGFA*) are the core targets of these four active ingredients, which helped reveal the antidepressant mechanism of SJC [35]. The Gan-Mai-Da-Zao Decoction (GMDZD) is an effective TCM prescription for post-stroke depression (PSD). Isorhamnetin, kaempferol, luteolin, naringin, and quercetin are the core active components of GMDZD. Network pharmacological analysis identified 203 potential targets to be screened for PSD treatment, including *AKT1*, *EGFR*, *JUN*, signal transducer and activator of transcription 3 (*STAT3*), *TNF*, and tumor protein 53 (*TP53*). Molecular docking analysis suggested that the core active components of GMDZD were closely bound to these core targets, further supporting the anti-PSD effect of GMDZD from the pharmacological mechanism. Moreover, GMDZD is widely enriched in a series of signaling pathways, such as hypoxia inducible factor-1 (HIF-1), TNF, and toll-like receptors, which may also participate in the antidepressant effects of GMDZD [36]. Clinical studies and *in vivo* experiments have widely confirmed that Xiao-Yao-San (XYS) has antidepressant effects. Seven of the main active ingredients of XYS are thought to be related to its antidepressant effects: abrin, aloin, emodin, glycomycin C, kaempferol, luteolin, paeoniflorin, and quercetin. Network pharmacology suggests that *AKT1*, *TP53*, and *VEGFA* may be key antidepressant targets of XYS and that the active ingredients in XYS have predictable regulatory relationships with these hub genes. *In vitro* experiments have also confirmed that XYS can reverse corticosterone-induced neurotoxicity and may have a neuroprotective effect by promoting Akt phosphorylation, which further validates the antidepressant components and pharmacological mechanism of XYS [37]. In summary, these studies indirectly demonstrate the antidepressant activity of luteolin (Table 1) [26–37].

4. Clinical trials

Although limited in quantity of the clinical trials, luteolin has shown neuroprotective effects in several controlled clinical studies and plays a role in the treatment of neuropsychiatric disorders. Buchanan et al. (NCT05204407) are currently investigating the therapeutic effects of luteolin (300 mg bid) administered over 12 weeks on schizophrenia and cognitive impairment and whether the neuroprotective effects of luteolin are mediated through anti-inflammatory and antioxidant mechanisms. A forthcoming randomized controlled clinical study by Assogna et al. [38] aims to evaluate the effects of daily luteolin supplementation at 250 mg twice daily for two weeks on memory function and has yielded promising results in a preliminary animal model. Frontotemporal dementia (FTD) is a severe neurodegenerative disease, and novel drugs that target neuroinflammation may aid in its treatment. A usable form of palmitoylethanolamide and luteolin (PEA-LUT), which has been shown to have anti-inflammatory and neuroprotective properties, has received attention for FTD-related neurodegenerative diseases. Lucia et al. (NCT04489017) are targeting FTD with PEA-LUT at an oral dose of 700 mg twice a day in a trial currently in clinical phase 2. Additionally, dietary supplementation with PEA-LUT at a dose of 700/70 mg twice daily for 8 weeks may improve GABAergic neurotransmission and long-term potentiation-synaptic plasticity in long corona virus disease (COVID) patients with cognitive complaints and fatigue. Dietary supplements containing luteolin and quercetin may improve clinical symptoms in children with autism spectrum disorders (ASD). Taliou et al. [39] instructed children with ASD to receive a dietary formulation containing two flavonoid compounds, luteolin (100 mg/capsule) and quercetin (70 mg/capsule), and quercetin glycoside rutin (30 mg/capsule), administered as one soft capsule per 10 kg body weight daily with food for 26 weeks. The results showed that patients in the treatment group had improved quality of life (Vineland Adaptive Behavior Scales) and daily living skills (Table 2) [38,39]. Although controlled clinical studies on luteolin in the treatment of depression are still lacking, combined with its anti-inflammatory, antioxidant, and neuroprotective effects, with the deepening of preclinical studies on the antidepressant effects of luteolin, we are anticipating a multicenter randomized controlled study on luteolin's antidepressant effects.

5. Antidepressant mechanisms of luteolin

5.1. Improvement of neurotransmitter levels

Monoamine neurotransmitters such as 5-HT, NE, and DA have a range of biological activities and play a central role in physiological responses of the CNS such as mood regulation, mental activity,

Table 1
Summary of studies on the antidepressant effect of the source of luteolin.

Source	Strains/cell lines	Models	Doses and administration	Duration	Behavioral evaluation	Molecular changes	Pharmacological effects	Refs.
Peanut shell	Male ICR mice	CMUS	100–900 mg/kg/day, p.o.	2 weeks	The sucrose water consumption ↑, the immobile time in TST and FST ↓, and Lachnospiraceae ↑	5-HT ↑, NE ↑, DA↑, neurotrophic factors ↑, IL-1β ↓, IL-6 ↓, TNF-α ↓, LPS ↓, ACTH ↓, and corticotropin releasing factor ↓	Anti-inflammation, regulate gut microbiome and hormones, and promote neurogenesis and neuroplasticity	[26]
Clerodendrum serratum Linn. leaves	Male Swiss albino mice	ARS	25 and 50 mg/kg/day, p.o.	7 days	The immobile time in TST and FST ↓	SOD activity ↓, CAT activity ↑, GPX activity ↓, MDA ↓, NE ↑, and 5-HT ↑	Anti-oxidation and regulate neurotransmitters	[27]
Rosmarinus officinalis	Male ICR mice; PC12 cells	Corticosterone-induced	50 and 100 mg/kg/day, p.o.; 50 μM	7 days; 48 h	The immobile time in TST ↓ and the cell viability ↑	MKP-1 expression ↓, MAPK phosphatase ↓, TH and PC mRNA expression ↑, NE ↑, DA ↑, 5-HT ↑, Ch ↑, and Ach ↑	Enhance neurotransmitters functions	[28,29]
Eremostachys laciniata (L) Bunge	Albino mice	–	0.1, 1, 3, 5, 7, 10, 12, and 15 mg/kg, i.p.	–	The immobile time in FST ↓	–	Sedative and calming effect	[30]
Danzhi-xiaoyao-San	Patients	Depressive patients	75.3 g/day, p.o.	4 weeks	HAMD-24 scores ↓, Proteobacteria ↑, Actinobacteria ↑, and Verrumcomicrobia ↑	Lysophosphatidic acid ↓	Regulate the metabolism of lysophosphatidic acid and the gut microbiome	[31]
Zhi-Zi-Hou-Po Decoction	Male ICR mice	–	81.4 g/day, p.o.	5 days	–	The combination with SLC6A4, GLO1, MAOB, and MTNR1A ↑	Regulate neurotransmitter receptors	[32]
Chaihu Shugan San	Male C57BL/6 mice	CUMS	2.7 g/kg/day, p.o.	6 weeks	Body weight of mice ↑, the sucrose water consumption ↑, and the immobile time in TST and FST ↓	$NeuN^{+}BrdU^{+}$ cells ↑, pPI3K↑, pAKT ↑, GSK3β ↓, pGSK3β-Ser9 ↑, and BDNF ↑	Promote neurogenesis	[33]
Shugan Jieyu Capsule	Network pharmacology	–	–	–	–	PTGS2, CASP3, IL-17, TNF, and MAPK	Anti-inflammatory and anti-oxidative stress	[34,35]
Gan-Mai-Da-Zao Decoction	Network pharmacology	Poststroke depression	–	–	–	Core gene STAT3, JUN, TNF, TP53, AKT1 and EGFR, regulation of TNF, HIF-1, and TLR pathways	Anti-inflammatory, regulate hormones, and neuroprotective effect	[36]
Formula Xiao-Yao-San	Network pharmacology	–	–	–	–	Three hub genes (AKT1, TP53, and VEGF)↑ and reverse the downregulated AKT phosphorylation	Regulate neuroendocrine function and neuro-immunity	[37]

–: no data. ICR: Institute of Cancer Research; CMUS: chronic unpredictable mild stress; p.o.: per os; TST: tail suspension test; FST: forced swimming test; 5-HT: 5-hydroxytryptamine; NE: norepinephrine; DA: dopamine; IL: interleukin; TNF: tumor necrosis factor; LPS: lipopolysaccharide; ACTH: adrenocorticotropic hormone; ARS: acute restraint stress; SOD: superoxide dismutase; CAT: catalase; GPX: glutathione peroxidase; MDA: malondialdehyde; PC: pheochromocytoma cells; MKP-1: mitogen-activated protein kinase phosphatase 1; MAPK: mitogen-activated protein kinase; TH: tyrosine hydroxylase; PC: pyruvate carboxylase; Ch: choline; Ach: acetylcholine; i.p.: intraperitoneal injections; HAMD-24: the 24-item Hamilton Depression Scale; SLC6A4: solute carrier family 6, member 4; GLO1: glyoxalase 1; MAOB: monoamine oxidase B; MTNR1A: melatonin receptor 1A Gene; NeuN: neuronal nuclei; BrdU: bromodeoxyuridine; pPI3K: phosphorylated phosphoinositide 3-kinase; pAKT: phosphorylated protein kinase B; , GSK3β: glycogen synthase kinase 3 beta; BDNF: brain-derived neurotrophic factor; PTGS2: prostaglandin endoperoxide synthase 2; CASP3: caspase 3; Core gene STAT3: signal transducer and activator of transcription 3; JUN: Jun proto-oncogene; TP53: tumor protein P53; AKT1: serine/threonine kinase 1; EGFR: epidermal growth factor receptor; HIF-1: hypoxia inducible factor-1; TLR: toll-like receptors; VEGF: vascular endothelial growth factor.

sleep, and stress response. Monoaminergic neurotransmission imbalances have been accepted as the most common cause of depression [40]. According to the monoamine hypothesis, depleted monoaminergic neurotransmitters can induce depression-like behaviors, while monoamine reuptake inhibitors can treat depression [41]. Reduced sensitivity of the postsynaptic membrane to monoamine neurotransmitters and decreased monoamine neurotransmitter receptors have also been reported in patients with depression [42]. Therefore, maintaining balanced monoamine neurotransmitters, increasing monoamine neurotransmitter levels, and improving postsynaptic membrane sensitivity to monoamine neurotransmitters are effective treatments for depression.

Preclinical research suggests that luteolin effectively exerts antidepressant and neuroprotective effects by inhibiting monoamine neurotransmitter reuptake to increase their levels in the brain (Fig. 3). Luteolin directly increases monoamine neurotransmitter levels. Luteolin administration improved depressive behavior in mice with posttraumatic stress disorder in the fear conditioning test and FST by increasing 5-HT levels. Additionally, luteolin regulates excessive HPA axis activation by reducing the production of corticosterone, which is one mechanism by which luteolin improves depressive behavior in mice [43]. Luteolin also inhibited the reuptake of monoamine neurotransmitters, indirectly increasing their levels of monoamine neurotransmitters. Zhu et al. [44] found that in the CUMS mice model with estrogen deficiency and *in vitro* primary hippocampal neurons, luteolin inhibited 5-HT reuptake by directly inhibiting monoamine transporters and indirectly regulating the gene expression of the plasma membrane monoamine transporter. Furthermore, luteolin can indirectly increase monoamine neurotransmitters by reducing the activity of enzymes that promote their elimination. Monoamine oxidase-A (MAO-A) is a key enzyme in 5-HT metabolism, and its activity decreases to promote 5-HT levels. For *in vitro* SH-SY5Y cells, MAO-A activity significantly decreased after luteolin intervention targeting the mitochondria, although the mRNA and protein expression levels of MAO-A were not significantly affected [45]. Therefore, either directly or indirectly increasing the monoamine neurotransmitter concentration in the synaptic cleft is an important mechanism through which luteolin exerts antidepressant and neuroprotective effects.

GABA is a naturally inhibitory neurotransmitter in the human nervous system that regulates synaptic transmission, thereby promoting neuronal development and preventing insomnia and depression [46]. The “5-HT-Glu/GABA long neural circuit” hypothesis posits that both monoaminergic and non-monoaminergic mechanisms are included in rapid-acting antidepressant mechanisms [47]. Several studies have shown that the inhibitory function of GABA and significant defects in GABA receptors decrease in the parahippocampal and cortical brain regions of patients with depression [48]. *In vivo* research has shown that luteolin produced antidepressant-like effects in mice, resulting in reduced immobility in the FST. Indeed, luteolin acts as a positive regulator of the GABAA receptor-chloride channel complex [49]. Luteolin's antidepressant effects may be mediated by improving GABA level deficiency and cortical GABAA receptor activity.

5.2. Synaptic function promotion

Synaptic plasticity represents the brain's fundamental ability to perceive, evaluate, and store complex information and respond appropriately and adaptively to subsequent relevant stimuli. This critical brain function plays a key role in the pathophysiology and treatment of various neurobiological disorders, including depression [50]. Among the findings of altered brain structure and function in patients with depression, the most consistent is structural deformation and impaired function in the hippocampus and prefrontal cortex (PFC) [51]. Studies in rodent models and humans have confirmed that exposure to stress such as depression reduces the number of synapses, atrophic neurons, and glial cells in the PFC and hippocampus [52]. Some antidepressant drugs, such as ketamine, alleviate depression through the rapid induction of synaptogenesis and the reversal of atrophy [53]. Therefore, promoting

Table 2
Clinical trials data of luteolin.

Clinical trial number	Start date	Study type	Recruitment status (phase)	Conditions	Interventions	Study title	Refs.
NCT05204407	June 13, 2022	Double-blind, placebo-controlled, randomized clinical trial	Recruiting (not applicable)	Schizophrenia and schizoaffective disorder	Dietary supplement luteolin (300 mg b.i.d. taken over 12 weeks)	Luteolin for the treatment of people with schizophrenia	–
NCT06047899	November 28, 2023	Randomized double-blind placebo-controlled counter-balanced	Not yet recruiting	Memory functions	Dietary supplement: luteolin	Influence of luteolin for two weeks on memory in healthy subjects	[38]
NCT04489017	June 1, 2019	Parallel assignment	Completed (phase 2)	Frontotemporal dementia	Palmitoylethanolamide and luteolin	Palmitoylethanolamide combined with luteolin in frontotemporal dementia patients. A randomized controlled trial	–
NCT01847521	December 2011	Single Group Assignment	Completed (phase 2)	Autism spectrum disorders	Dietary supplement: luteolin, quercetin and rutin combined in a capsule	Effects of the anti-inflammatory flavonoid luteolin on behavior in children with autism spectrum disorders	[39]
NCT05311852	August 16, 2021	Double-blind randomized placebo-controlled study	Completed (not applicable)	Fatigue, cognitive deficit, COVID-19, and neurophysiologic abnormality	Dietary supplement: palmitoylethanolamide co-ultra-micronized with antioxidant flavonoid luteolin (PEA-LUT)	Effects of PEA-LUT on frontal lobe functions and GABAergic transmission in long-COVID patients	–
NCT04468854	January 1, 2019	Randomized double-blind placebo-controlled counter-balanced	Terminated (not applicable)	Memory functions	Dietary supplement luteolin (500 mg luteolin per day for oral administration for 7.5 days)	Influence of luteolin on memory in healthy subjects	–

–: no data. COVID-19: corona virus disease 2019; PEA-LUT: palmitoylethanolamide co-ultra-micronized with antioxidant flavonoid luteolin.

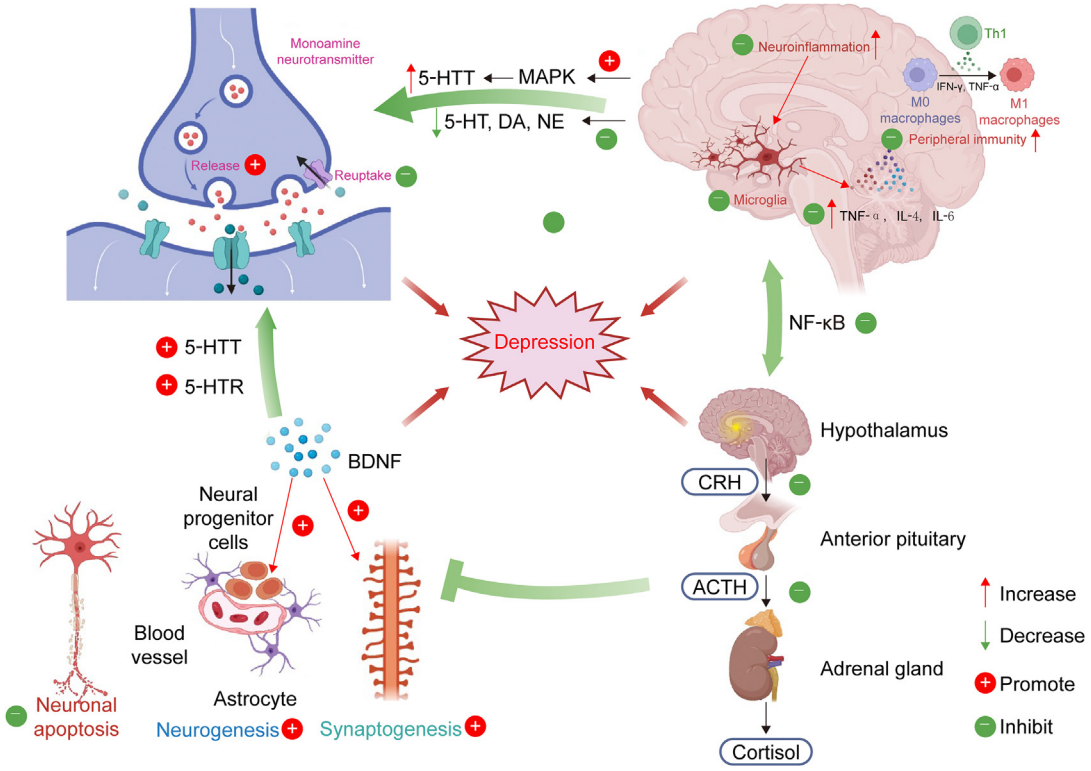

Fig. 3. The antidepressant mechanisms of luteolin. Luteolin acts as an antidepressant by raising monoamine neurotransmitter levels and promoting synaptogenesis and neurogenesis while inhibiting neuronal apoptosis. It also modulates the immune response and reduces inflammation, impacting the hypothalamic–pituitary axis. 5-HTT: 5-hydroxytryptamine transporter; 5-HTR: 5-hydroxytryptamine receptor; MAPK: mitogen-activated protein kinase; 5-HT: 5-hydroxytryptamine; DA: dopamine; NE: norepinephrine; IFN-γ: interferon gamma; TNF-α: tumor necrosis factor alpha; IL: interleukin; BDNF: brain-derived neurotrophic factor; CRH: corticotropin-releasing hormone; ACTH: adrenocorticotropic hormone.

synaptic regeneration, improving synaptic function, and repairing damaged nerve cells have become innovative strategies for treating depression [54].

Synaptogenesis is subject to the interplay between complex signaling pathways, including neurotrophic factors, estradiol levels, neuroinflammation, and glutamate (Glu) synthesis and reuptake. Studies have shown that luteolin helps regulate these pathways and plays an active role in synaptogenesis. An *in vivo* study by Cheng et al. [55] showed that luteolin treatment protected against anhedonia decreased spontaneous activity, and hypokinesis in noise-exposed mice. Luteolin decreases the levels of proinflammatory cytokines and increases the levels of brain-derived neurotrophic factor (BDNF) and its downstream phosphorylated mechanistic target of rapamycin (p-mTOR), synaptic proteins synaptophysin (SYN), and PSD-95, thereby affecting synaptic function and morphology. In a rat model of late-onset depression (LOD), the therapeutic effects of luteolin were noteworthy: luteolin improves cognitive function and depression-like behavior in LOD rats. Mechanistically, luteolin promotes synaptogenesis by evaluating the levels of five important axon guidance molecules in the cerebrospinal soluble ephrin-A5 (fluid-EFNA5), ephrin type-B receptor 4 (EPHB4), ephrin type-A receptor 4 (EPHA4), semaphorin 7A (SEMA7A), and netrin-G (NTNG) [56]. Moreover, luteolin was shown to reverse the decline in the number of neurons expressing calbindin and dendritic loss induced by cobalt chloride. Immunohistochemistry reveals that luteolin intervention increases the astrocytic expression of glial fibrillary acidic protein (GFAP) and pronounced dendrites in Purkinje cells [57]. Thus, evidence overwhelmingly suggests that luteolin regulates synaptic function via different pathways to achieve antidepressant and neuroprotective effects.

5.3. Inhibition of OS

OS is an imbalance between reactive oxygen species (ROS) production and the cellular antioxidant capacity. Under normal conditions, a sufficient cell response to ROS production is essential to prevent further oxidative tissue damage or cell death from enzymatic and non-enzymatic antioxidant defenses to support redox homeostasis [58]. However, excessive ROS production and defects in the antioxidant defense system can disrupt cellular redox homeostasis, thereby activating proinflammatory signals including MAPK, PI3K/AKT, and NF-κB, and subsequently destroying important macromolecules and inducing cellular apoptosis [59]. OS and depression share a close relationship. Research indicated that increased ROS production is found in patients with depression compared to those without depression, such as, 8-hydroxy-2′-deoxyguanosine and F2-isoprostanes [60]. Antioxidant activity is reduced in patients with depression and is associated with depressive symptom severity [61]. Furthermore, patients with depression exhibit mitochondrial defects and dysfunction, which is the major source of ROS and site of apoptotic and necrotic processes [59]. Evidence from animal studies suggests that antioxidant therapy can be successfully used as an effective adjunct to antidepressants [62].

Several neurological injury models have shown that luteolin can inhibit excessive ROS production and maintain the stability of the cellular redox system. For example, in chronic neuropathic pain-induced mood disorders (e.g., depression), behavioral studies show that luteolin can effectively relieve thermal hyperalgesia and cold allodynia. In addition, luteolin can dose-dependently regulate the OS markers (catalase (CAT), nuclear factor erythroid 2-related factor 2 (Nrf2), SOD, and MDA) and proinflammatory cytokines

(TNF-α, IL-1β, and IL-6) in the hippocampus cortex (HPC) and PFC of animals to treat depression [63]. In research on rats exposed to cobalt chloride, luteolin revealed an overproduction of H_2O_2 and MDA, as down-regulation of key antioxidant enzymes, including GPX, SOD, and glutathione-*S*-transferase (GST), to inhibit damage to Purkinje neurons in the cerebellum. Furthermore, luteolin restored acetylcholinesterase activity to improve cobalt chloride-induced impairment of learning, memory, and exploration activities [57]. These results strongly suggest that luteolin may play a role in treating depression via the anti-OS mechanism.

5.4. Inhibition of neuroinflammation

Neuroinflammation is a defense response of the CNS against biological, physical, chemical, and other damage factors. Peripheral inflammatory cytokines can enter the CNS through the blood-brain barrier (BBB) or specific transporters [64]. In addition, the CNS has its own "local immune system", which is primarily mediated by microglia and astrocytes [65]. In normal physiological environments, microglia regulate cytokines and inflammatory responses, release neurotrophic factors that promote neuronal growth, and participate in neurogenesis, synapse generation, neuro-nutrition, phagocytosis, and clearance [66]. However, when microglia are overactivated, they inevitably damage normal neurocytes. Emerging evidence indicates that neuroinflammation and excessive microglial activity are involved in the pathogenesis of depression [67]. Antidepressants, such as SSRIs and SNRIs, reduce microglial reactivity and inflammatory cytokines levels, mainly including TNF-α, IL-1β, and IL-6 in patients with depression [68].

Luteolin can directly inhibit central nervous inflammation and immune response. In mice with lipopolysaccharide (LPS)-induced C57BL/6, luteolin significantly inhibited the NF-κB pathway through upregulation of A20 and Nrf2 in microglia and further demonstrated that A20 can exert its function as a downstream factor of Nrf2 [69]. Luteolin increases the sucrose preference of mice, decreases immobility time in the FST, and inhibits IL-1β and IL-6 production in mouse brains. In a CUMS comorbid dry-eye model, luteolin significantly inhibited the activation of microglia, reduced TNF-α, IL-1β, IL-6, and IL-18 production, and regulated the signaling pathway silencing information modulator related enzyme 1 (Sirt1)/NF-κB/NOD-like receptor protein 3 (NLRP3) to in improve symptoms of dry eye and depression [18]. Cheng et al. [55] found that luteolin could reverse the up-regulation of IL-1β, IL-6, and TNF-α in the hippocampus and prefrontal cortex of mice with noise-induced depression while improving synaptic plasticity impairments by inducing BDNF expression. Luteolin was also shown to promote differentiation in human neural stem cells into astrocytes through regulating global gene expression and biological processes *in vitro* and *in vivo*, as well as decreased the levels of IL-6, TNF-α, and corticosterone [70]. Furthermore, in a mouse model of Alzheimer disease (AD), luteolin treatment increased global activity in the tail suspension test (TST) and decreased immobility time in the FST. Further cytological analysis revealed that luteolin inhibited the expression of activating transcription factor 4 (ATF4) and presenilin-1, protecting neurons from Aβ-induced injury [71]. These *in vitro* and *in vivo* experiments demonstrate the antidepressant activity of luteolin through the inhibition of neuroinflammation.

5.5. Inhibition of apoptosis and autophagy

Apoptosis and autophagy are widely considered programmed cell deaths *in vivo* and are particularly essential for normal cell renewal, nervous system development, and maintenance of homeostasis and energy supplies [72]. Apoptosis is characterized by DNA fragmentation, proteolysis, and morphological changes [73]. Autophagy is the main intracellular pathway for the delivery and degradation of long-lived cytoplasmic proteins and damaged organelles in lysosomes [74]. However, excessive apoptosis and autophagy are important factors in depression onset and progression [75]. Autophagy and apoptosis are critical regulators of the aging process, which is a multifactorial phenomenon involving complex interactions between genetic, environmental, and lifestyle factors [76]. Autophagy can promote cell survival by removing damaged components and preventing the accumulation of senescent cells. Conversely, autophagy impairment can lead to the development of senescence. Similarly, apoptosis can eliminate senescent cells, while dysregulated apoptosis can contribute to the senescence of cells [77]. Apoptosis is closely related to important cytokines, including apoptotic protease activator 1, Bcl-2 family, caspase family proteins, NLRP3 inflammasome, p62, tumor suppressor genes, and Fas signal transduction [78]. Several studies have shown that the neuroprotective effects of luteolin are related to the regulation of a series of anti-apoptotic and anti-autophagy signaling pathways.

In a rat model of breast cancer-associated depression, luteolin significantly increased the immobility time in the TST and FST, suggesting an antidepressant effect [79]. *In vitro* experiments provided further evidence supporting anti-apoptosis as the antidepressant mechanism of luteolin by showing that luteolin could significantly inhibit apoptosis and reduce NLRP3, caspase-1, and gasdermin D-N levels in hippocampal neurons [79]. Luteolin also improved Bcl-2/Bax imbalance and increased BDNF levels in the hippocampus and prefrontal cortex neurons of a chronic constrictive injury rat model, demonstrating antidepressant, anxiolytic, and neuroprotective effects [63]. In a depression-associated dry eye model, luteolin enhanced cell viability and reversed changes in levels of apoptosis and inflammation-related proteins involving Sirt, Bcl-2, NF-κB, NLRP3, TNF-α, Ac-caspase-1, gasdermin D (GSDMD)-N, p53, and cleaved IL-1β expressions in hippocampi and corneal tissues to protect against apoptosis [18]. When hippocampal neurogenesis and neuroplasticity were evaluated in a mouse model of depression-like behavior induced by corticosterone, immunostaining and Western blot analysis suggested that luteolin treatment increased BDNF and Bcl-2 expression, indicating a regulatory effect of luteolin on anti-apoptosis [80]. In the CUMS model, the ratio of microtubule associated protein 1 light chain 3 (LC3)-II/I was significantly decreased, and the expression of p62 protein was markedly increased, indicating a decrease in autophagic activity in the rat hippocampus, while the autophagic activity was over-activated in the PFC. Luteolin treatment inhibited cellular autophagy in the PFC, while increased in autophagic activity in the hippocampus of CUMS rats. The bidirectional regulation of autophagy in different brain regions may exert a crucial role in the therapeutic effects of luteolin on depression, as autophagy is closely related to various cellular processes, including lipid metabolism and synaptic function. Furthermore, luteolin regulated abnormal glycerophospholipid metabolic pathways to treat autophagy disturbances and maintained the functional integrity of membrane proteins involved in synaptic neurotransmission, thereby helping to improve synaptic formation, transmission, and plasticity [81]. However, the exact mechanisms of luteolin's influence on autophagy in CUMS rats require further investigation.

5.6. Endoplasmic reticulum (ER) stress inhibition

ER is a cytoplasmic membrane system consisting of interconnected tubes, flat sacs, and vesicles. The main function of the ER is to participate in the synthesis, processing, packaging, and transportation of proteins and lipids, and it is especially active in nerve cells. Accumulation of unfolded or incorrectly folded proteins in the

ER can lead to ER stress (ERS) [82]. HSP90 protein, a member of the heat shock protein family involved in protein folding in the ER, is related to the pathogenesis of depression and response to antidepressant drugs [83]. In addition, the expression of ERS-related proteins significantly increased in an animal model of caries-associated depression, and the expression of these proteins decreased after antidepressant treatment [84]. The antidepressant SSRI fluvoxamine also reduces ERS [85]. Histone deacetylase (HDAC) inhibitors are promising substances for antidepressant treatment [86], as they can induce glucose-regulated protein 78 (GRP78)/immunoglobulin heavy chain-binding protein (BiP) expression [87]. This indicates that the antidepressant effects of HDAC inhibitors may be achieved through changing ERS levels. These findings suggest a potential association between depression onset and ERS.

The antidepressant effects of luteolin are associated with decreased ERS. *In vitro* SH-SY5Y cells cultured with tunicamycin and luteolin showed significantly increased expression of the 78 kDa glucose-regulated and 94 kDa glucose-regulated proteins, which reportedly have a protective effect on ERS-induced cell death [88]. In APP23, with an AD mice model, behavioral analyses using the TST and FST showed that depression-like behaviors were ameliorated in the luteolin-treated AD and corticosterone-induced depression mice models. This antidepressant effect was associated with luteolin inhibiting LPS-induced ERS and decreasing CD68 levels in the brain [71]. These findings suggest that luteolin prevents ERS and protects cells from ERS-induced damage, thereby facilitating an antidepressant effect.

5.7. Up-regulation of the folate transport

Folate is a key regulator of hippocampal neurogenesis, and adequate folate levels are particularly important for neurodevelopment [89]. An increasing number of studies have focused on the mechanism of folate deficiency in depression, especially in the elderly population [90]. Studies have shown that folate deficiency, such as exposure to the dihydrofolate reductase inhibitor methotrexate, reduces hippocampal neural stem cell proliferation and is accompanied by an increased rate of apoptosis in neonatal neurons, leading to hippocampal volume atrophy and affecting memory and cognitive function [91]. In an aged rat model of CUMS, the levels of 5-methyltetrahydrofolate, zone of occlusion protein 1, protic-coupled folate transporter, and reduced folate carrier protein in the cerebrospinal fluid and hippocampus decreased. However, treatment with luteolin reversed these effects. *In vitro* experiments have shown that luteolin significantly increases the viability of injured neural stem cells, and attenuates dysfunctional neurogenesis and neuronal loss [92]. These results suggest that luteolin can ameliorate the LOD-like behavior induced by CUMS by enhancing folate brain transport.

6. Identification of hub genes and candidate pathway of luteolin antidepressant by integrated bioinformatic analysis

6.1. Targets of luteolin in depression treatment based on network pharmacology

All depression-related targets were standardized by searching the Therapeutic Target Database, OMIM, DigSee, and Comparative Toxicogenomics Database. To improve data accuracy, low-scoring disease-associated targets were removed from the database search results. After deleting duplicates, 1,437 depression-related targets were identified.

One hundred predicted targets of luteolin were retrieved through PharmMapper and SwissTargetPrediction, and 59 predicted targets were screened using a standard deviation multiple greater than 1.5. By overlapping the 59 predicted luteolin and depression-associated targets (1,437), 41 potential antidepressant targets of luteolin were identified (Fig. 4A). The 41 screened results were entered into the DAVID database for GO and KEGG pathway enrichment analyses. A bubble map was drawn according to *P*-value size, and the first 10 paths with the lowest *P*-values were selected for visualization (Figs. 4B–D). For enrichment of the KEGG pathway, the screening condition was that the number of enriched targets was greater than or equal to five. The bubble chart of the first 10 pathways sorted by *P*-value is shown in Fig. 4E.

6.2. Protein-protein interaction (PPI) network and prediction of core targets

To better explore the protein interactions between luteolin and depression targets, we analyzed the PPI network of 41 cross-target sites using the STRING database (https://string-db.org/) and constructed a PPI regulatory network with 41 nodes and 183 edges using Cytoscape software, as shown in Fig. 5. We used the Degree and MCODE algorithms in the Cytoscape 3.9.1, plugin of Cytoscape software to select the core targets, and sorted the predicted luteolin and depression-associated targets in order of centrality from highest to lowest. Five targets (epidermal growth factor receptor (EFGR), insulin-like growth factor 1 receptor (IGF1R), AKT1, PTGS2, and estrogen receptor alpha (ESR1)) with the highest centrality were selected for molecular docking analysis (Fig. 5).

6.3. Molecular docking

Molecular docking results showed that the binding energy of the five target proteins with luteolin was less than −3 kcal/mol, indicating that they had good interaction with luteolin. Five target proteins with the lowest docking energies were selected, and the specific conditions and binding energies of the docking were determined using PyMol 2.4. The docking energies of luteolin with EGFR, IGF1R, AKT1, PTGS2, and ESR1 were −4.24, −4.66, −4.87, −4.91, and −4.49 kcal/mol, respectively. This suggests that they interact well with luteolin and may be important therapeutic targets for the antidepressant effects of luteolin.

6.4. GO and KEGG enrichment analysis of luteolin in the treatment of depression

GO and KEGG enrichment analyses of the 41 intersection targets were conducted. In $P < 0.01$, the number of enriched genes ≥ 3 was the screening condition, and a total of 2,422 GO portals and 193 KEGG pathways were obtained. GO enrichment results included biological process (BP), cell composition (CC), and molecular function (MF). The first 10 items of the three aspects were screened according to the *P*-value and a histogram was drawn, as shown in Fig. 4. In terms of biological processes, intersection targets were mainly enriched in the modulation of chemical synaptic transmission, regulation of trans-synaptic signaling, response to OS, protein autophosphorylation, cellular response to chemical stress, and response to amyloid beta. In terms of cellular components, intersection targets were mainly enriched in the vesicle lumen, secretory granule lumen, cytoplasmic vesicle lumen, apical part of the cell, and nuclear envelope. In terms of molecular functions, the intersection targets were mainly enriched in steroid binding, hormone binding, transcription coactivator binding, transcription cofactor binding, and nuclear receptor activity.

Antidepressants reverse the negative effects of stress and depression on synaptic function, increase plasticity, enhance neurotransmission, and promote the formation of new synapses in stress-sensitive brain regions [52]. Almost all known

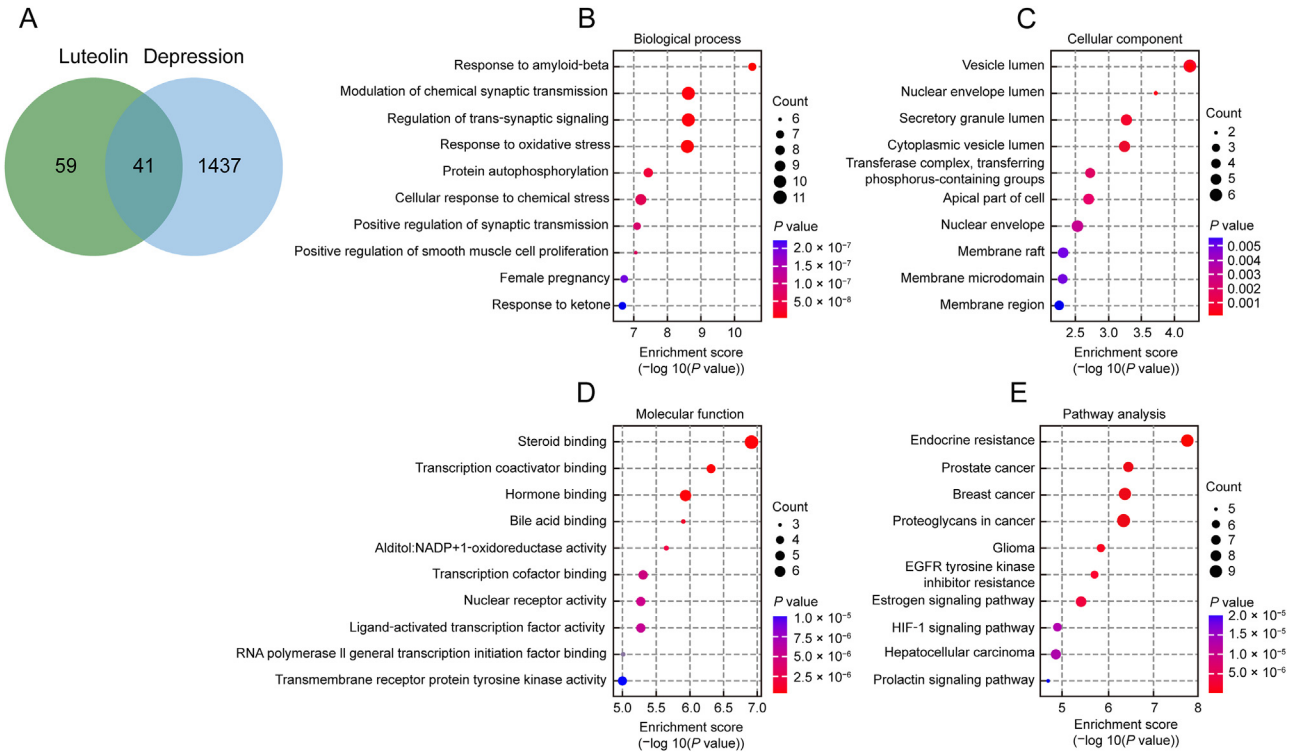

Fig. 4. Network pharmacologic and bioinformatics analysis of luteolin for depression. (A) Venn diagram of depression-related targets and predicted targets of luteolin. Drug-disease targets of luteolin and depression, (B–D) Gene ontology (GO) enrichment analysis (Top 10) includes biological processes (BP) (B), cellular components (CC) (C), and molecular functions (MF) (D). (E) Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of 41 screening results for luteolin treatment of depression. The horizontal axis represents the enrichment fraction, and the different colors represent the *P*-value. The redder the color, the lower the *P*-value, and the more significant the difference. The size of the dot indicates the number of genes enriched in the pathway; the larger the dot, the higher the number of genes enriched in the pathway. EGFR: epidermal growth factor receptor; HIF-1: hypoxia-inducible factor 1.

antidepressants have varying degrees of synaptic protective properties, suggesting that synaptic remodeling plays a key role in the pathophysiology of depression [93]. The hippocampus was the first brain structure associated with morphological changes after depression and stress [94]. Previous studies have shown that glucocorticoids induce cell death and hippocampus atrophy [95]. Antidepressants enhance the plasticity of the stress-sensitive circuits and promote synaptogenesis [96]. These new synapses play specific roles in the long-term maintenance of the depressive effects of antidepressants, prolonging remission and preventing relapse [93].

OS and response to amyloid-beta biological processes involved in the pathogenesis of depression [97]. OS has been shown to be an important factor in the pathogenesis of depression. Increased OS formation in the brain can exacerbate the development of depression through mitochondrial dysfunction and membrane lipid damage. Recent evidence suggests that OS plays a crucial role in the development of depression progression [98]. Therefore, drugs with antioxidant and anti-inflammatory effects may alleviate depressive behaviors [99]. Patients with a history of depression have significantly increased levels of amyloid plaques and neurofibrillary tangles in the brain, and those with depression and amyloid deposition are more likely to develop dementia [100]. In addition, elevated plasma amyloid levels in patients with depression may exacerbate dementia.

The dephosphorylation of protein phosphatases plays a key role in many aspects of neuronal function by hydrolyzing and catalyzing phosphate groups in proteins, including key steps involved in regulating synaptic communication, and can regulate synaptic plasticity by catalyzing the dephosphorylation of most phosphoserines and phosphothreonine in cells at the synaptic site, thus participating in the regulation of depression [101]. Protein phosphatase 1 (PP1) may regulate neuro-excitability through dephosphorylation or other mechanisms to regulate depression and depression-related behaviors [102]. Interventions in the process of protein phosphatase dephosphorylation and regulation of PP1 expression may provide ideas for the development of antidepressant drugs [103].

Neurosteroid hormones are synthesized from cholesterol in glial cells through a series of enzymatic reactions, mainly involving dehydroepiandrosterone, pregnenolone, progesterone, and tetrahydroprogesterone, and exert antidepressant-like behavioral effects by binding to GABA receptors [104]. Antidepressants promote the increased synthesis of neurosteroid hormones, which counteract cortisol/ketone-induced damage and regulate stressed mood and depression-like behavior [105].

For enrichment of the KEGG pathway, the intersection targets were mainly enriched in endocrine resistance, the estrogen signaling pathway, EGFR tyrosine kinase inhibitor resistance, and the HIF-1 signaling pathway, which may be the key pathways of luteolin in the anti-depressant effects.

Neuroendocrine functions mainly include the HPA, hypothalamic pituitary thyroid (HPT), and hypothalamic pituitary gonadal axes [106]. Dysfunction of the three major HPT organ systems causes symptoms of depression. It mainly manifests as a hyperfunction of the HPA axis, which is related to negative feedback adjustment disorder of the HPA axis. Excessive secretion of corticotropin-releasing hormones (CRH) in patients with depression increases CRH in the blood, cerebrospinal fluid, and metabolites, which downregulate the CRH receptor and cause the loss of the action site of excessive secretion of CRH, resulting in a vicious

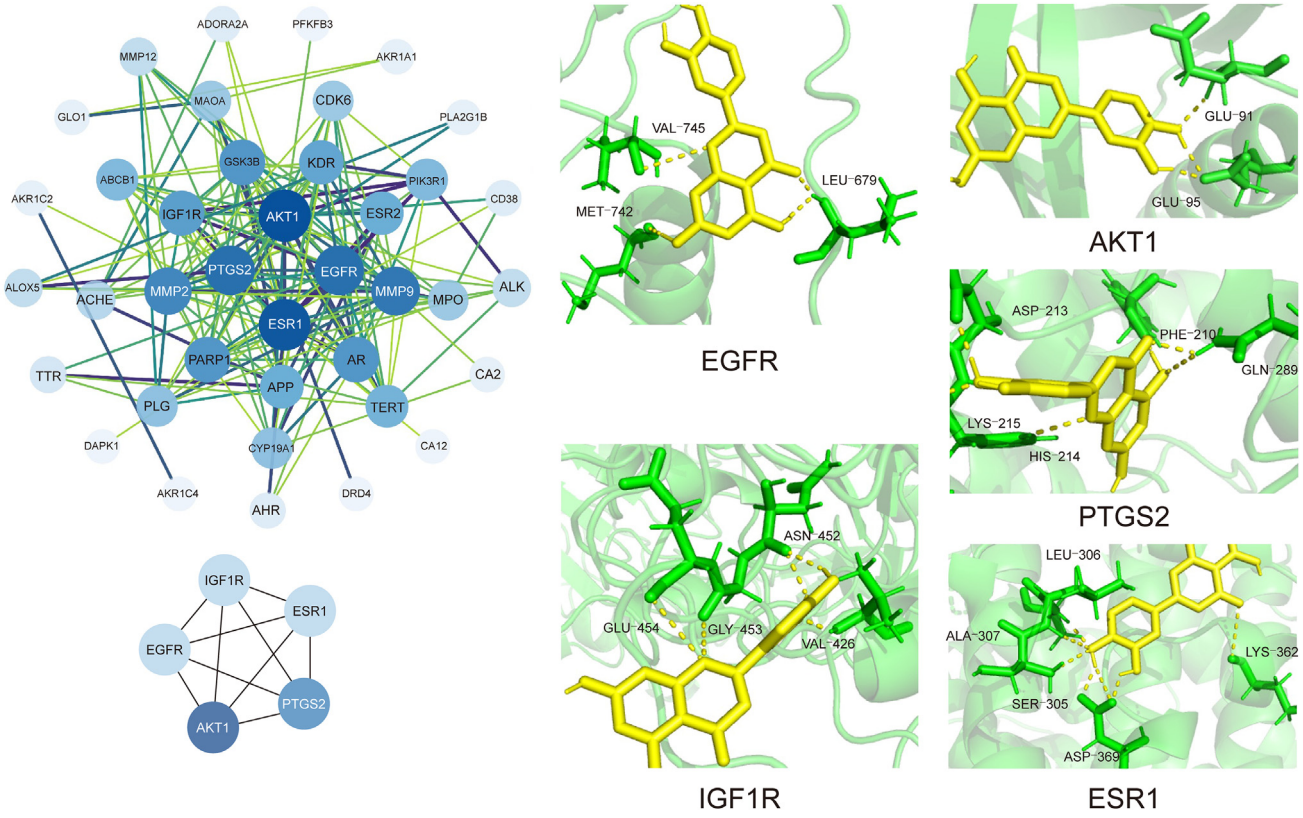

Fig. 5. Protein-protein interactions (PPI) network of depression-related targets and predicted targets of luteolin. The PPI network contains 41 key targets, and 5 hub genes (epidermal growth factor receptor (*EGFR*), insulin-like growth factor 1 receptor (*IGF1R*), AKT serine/threonine kinase 1 (*AKT1*), prostaglandin-endoperoxide synthase 2 (*PTGS2*), and estrogen receptor alpha (*ESR1*)) was identified by Cytoscape. Molecular docking analysis of these hub genes obtains promising binding energy, indicating a good docking effect.

cycle of increasing CRH in the body and eventually producing depressive symptoms [107]. In addition, related studies have found that depressive HPT is also dysfunctional, manifested by the insensitivity of thyroid-stimulating hormones to the feedback of thyrotropin-releasing hormones rather than thyroid dysfunction, resulting in insufficient thyroid hormone secretion [108]. Estrogen may play an antidepressant role via the 5-HT system. Estrogen binding with central receptors can enhance the postsynaptic 5-HT effect, increasing the number of 5-HT receptors and transport and absorption of neurotransmitters [109]. A decrease in estrogen levels causes a decrease in 5-HT concentration and activity in CNS, resulting in depression [110]. Luteolin may be involved in neuroendocrine regulation and play an antidepressant role via endocrine mechanisms.

Estrogen is a sex hormone mainly produced by the ovaries of female animals. Estrogen not only plays an important role in the reproductive system but also affects the development and activities of the CNS and autonomic nervous system, and is closely related to individual learning, memory, and behavior [111]. Moreover, estrogen can influence the course of depressive disorders by regulating various neurotransmitters such as Glu, GABA, 5-HT, and DA [112]. Kondo et al. [113] showed that estrogen can exert a positive regulatory role through the N-methyl-d-aspartic acid (NMDA) receptor in the postsynaptic membrane, thereby promoting the release of synaptic Glu and increasing the expression of the NMDA receptor and its sensitivity to Glu. Estrogen can also inhibit the degradation of monoamine oxidase and promote increased tryptophan hydroxylase levels, thereby increasing serum 5-HT content [114]. Estrogen may also play a role in depressive disorders through the HPT axis. The interaction of sex steroid hormones and BDNF plays a unique role in the regulation of NMDA receptor expression, which is dependent on the dorsal and ventral regions of the hippocampus, suggesting that estrogen and thyroid hormones may be linked through BDNF [115]. Estrogen can regulate the transcription of BDNF; therefore, it can be speculated that thyroid hormones and estrogen may have some relationship with depression [116]. Estrogen abnormalities play an important role in the occurrence and development of depressive disorders. *In vitro* studies have shown that luteolin promotes aromatase protein degradation and inhibits estrogen biosynthesis in aromatase-expressing HEK293A cells [117]. Luteolin also regulates estrogen signaling in human breast cancer cells [118], suggesting that it may improve depression by regulating estrogen levels.

The pathophysiological mechanism of depression is related to increased neuroinflammation, and overactivation of EGFR can lead to neuroinflammation. Hou et al. [119] found that depressed model mice induced by the increased EGFR cell surface expression induced by propofol could improve depression-like behavior by reducing the expression of EGFR on the cell surface by irisin. Anson et al. [120] demonstrated the inhibitory effects of luteolin on downstream signaling molecules activated by EGFR, especially the AKT and MAPK signaling pathways. Luteolin also plays an anticancer role by inhibiting EGFR and promoting cell survival, suggesting that EGFR and its signaling pathways may be antidepression targets of luteolin [121].

HIF-1 plays an important role in the pathophysiological processes of brain damage and several vascular diseases [122]. HIF-1 is a major regulatory factor in maintaining the stability of oxygen in the body and an important transcription factor in encoding response genes in the body during hypoxia, which promotes the activation of the *VEGF* gene expression promoter [123]. Research on the expression of HIF-1 in depression is still in the early stages;

However, a study has shown that HIF-1 expression is upregulated in the brain tissue of animal models of depression [124]. As a nuclear transcription factor induced by hypoxia, HIF-1 may be involved in mediating hypoxia in vital organ tissues during the pathological process of depression [125]. Inhibitors of HIF-1 activity can improve the degree of BBB injury [126]. Luteolin induces a decrease in HIF-1 transcriptional activity in colon cancer cells [127], suggesting that it may be a useful therapeutic agent for treating depression.

The molecular docking results showed that luteolin has a desirable regulatory relationship with insulin-like growth factor 1 receptor (IGF1R), AKT1, PTGS2, ESR1, and EGFR. IGF1R is a protein that belongs to the insulin-like growth factor receptor family and plays an important role in signaling within cells, while also being involved in cell growth, differentiation, and survival [128]. As part of the signaling pathway, IGF1R is involved in regulating neuronal growth and synaptic connections, which in turn affects neuronal function [129]. First et al. [130] showed that chronic mild stress (CMS) reduced IGF1R levels in the hippocampus, whereas IGF1R levels returned to a normal range after fluoxetine treatment, and were associated with behavioral improvements in a CMS-induced rat model of depression, suggesting that IGF1R may be involved in the treatment mechanism of antidepressants.

AKT1 is an important signal-transduction protein kinase involved in the regulation of various cellular processes including cell survival, proliferation, differentiation, and metabolism [131], and a key component of the PI3K/AKT signaling pathway. In a CUMS model, Lu et al. [132] found that the levels of AKT and mTOR in the hippocampus of mice were downregulated, and after treatment with the selective agonist GLYX-13 of the NMDA receptor, depression-like behavior and molecular changes in the hippocampus were reversed in the mice. Subsequently, Liu and his team further showed that after CUMS, the phosphorylation levels of AKT and mTOR in the hippocampus and prefrontal cortex of mice were significantly reduced, and resveratrol treatment normalized these parameters [133]. Considering the important role of AKT/mTOR signaling inhibition in antidepressants, the luteolin-driver regulation of AKT may provide new clues for the development of antidepressants.

PTGS2, also known as cyclooxygenase-2 (COX-2), is an enzyme associated with inflammation and pain. It regulates the metabolism of arachidonic acid in the body by converting it into a series of prostaglandins that play important roles in the inflammatory response and other physiological processes [134]. COX-2 expression is associated with inflammatory activity in the CNS and is thought to be involved in the pathological processes of several acute and chronic neurodegenerative disorders [135]. COX-2 not only interacts with neurotransmitters such as ACH, 5-HT, and Glu but also participates in the immune and inflammatory responses of the CNS through prostaglandin E 2 (PGE2) [136]. An early study showed that restraint stress for 2–6 h can increase the expression of COX-2 in the cerebral cortex and hippocampus [137]. PGE2 production is increased, and COX-2 expression is enhanced in depression. The administration of celecoxib, a selective COX-2 inhibitor, improved depressive behavior in experimental rats by altering age-dependent increases in the levels of proinflammatory cytokines and anti-inflammatory corticosterone in the hippocampus [138]. Therefore, anti-inflammatory therapy will be a new avenue for depression treatment, and luteolin may become a new antidepressant and COX-2 regulator.

ESR1 is a nuclear receptor that binds to estrogen inside cells and regulates gene transcription. This receptor is widely expressed in the reproductive system and other tissues and involved in various physiological processes, including reproduction, metabolism, and neuroprotection [139]. ESR1 affects brain function and plays an important role in depression. ESR1 has previously been identified as a pathogenic gene for post-traumatic stress disorder (PTSD) and depression as well as a risk factor for suicidal behavior in veterans. Estrogen can promote neuronal cell survival, reduce neuronal damage, protect neuronal cells from neurotoxins, and enhance synaptic transmission and neurogenesis, which is one reason for sex differences in the incidence of depression [140]. We calculated the efficacy of the possible targets of luteolin in the treatment of depression, which may be further validated by *in vitro* and *in vivo* depression validation experiments in the future (Table 3) [18,44,45,49,55–57,63,69–71,79–81,88,92,115]. The molecular docking results for luteolin are presented in Table 4.

7. Characteristics of luteolin

7.1. Physicochemical properties and pharmacokinetics of luteolin

Luteolin has a C6-C3-C6 structure containing two benzene rings and one oxygen-containing ring with a C2-C3 carbon double bond. Hydroxyl moieties at the 5, 7, 3′, and 4′ carbon positions and double bonds at the 2 and 3 positions of luteolin are responsible for its various pharmacological effects [141]. Luteolin exists in the form of aglycones or glycosides. Luteolin aglycone (LA) is lipophilic and absorbed by intestinal cells. Luteolin glycosides (LG) are converted to LA in the intestine by hydrolyzing the glycosides to LA by lactase phlorizin hydrolase in the brush border intestinal membrane. Luteolin monoglucuronate is hydrolyzed to LA by β-glucosidase via the sodium-dependent glucose transporter-1. LG is also hydrolyzed to LA by certain gut microbiota; therefore, luteolin bioavailability varies depending on the distribution of gut microbiota [142]. Study has suggested that only small amounts of luteolin are present in urine and feces, indicating that the majority of luteolin may be metabolized into other compounds [143]. Luteolin can be converted into glucuronides as it passes through the intestinal mucosa, and free luteolin, luteolin conjugates, and methylated conjugates have been detected in rat and human plasma after administration [144]. Following oral administration of luteolin to rats, both luteolin and luteolin-7-*O*-glucoside metabolites are found in plasma samples, while luteolin metabolites such as luteolin-4′-*O*-glucuronide and luteolin-7-*O*-glucuronide are also detected in the liver, kidneys, and small intestine, which may be associated with the bioactivity *in vivo* [145]. These findings reveal that luteolin and its glucosylated forms may be metabolized to produce methylated, sulfated, and/or glucuronidated metabolites through Phase II metabolism. Subsequently, these metabolic products can enter the systemic circulation or be returned to the small intestine via the enterohepatic circulation.

Due to the poor stability and low absorption rate of luteolin, its bioavailability in the body is very low. The oral bioavailability of luteolin in mice is 26% ± 6%, which is higher than that of luteolin-7-*O*-glucoside (approximately 10% ± 2%) [146]. Luteolin-7-glucoside is primarily hydrolyzed into luteolin in the gastrointestinal tract, thereby being effectively absorbed into the systemic circulation. Moreover, coexisting compounds such as terpene chrysin may stimulate the intestinal absorption of luteolin and enhance its bioavailability [147]. Some pharmaceutical methods, such as polymeric micelles, cyclodextrin complexation, and phospholipid complexation, can also prolong the circulation time by retarding the degradation of luteolin in the blood, thereby improving its solubility and bioavailability [148]. Study using nanoparticle drug delivery systems have found that the bioavailability of luteolin-loaded nanoparticles is about five times that of free luteolin and increases the plasma concentration of luteolin [149]. Luteolin can cross the BBB; after peripheral injection, free luteolin can be detected in both the blood and brain tissue [150]. However, current

Table 3
Summary of *in vivo*/*in vitro* studies on the anti-depression effect of luteolin.

In vivo/vitro	Strains/cell lines	Models	Doses and administration	Duration	Behavioral evaluation	Molecular changes (Tissue/Cells)	Pharmacological effects	Refs.
In vivo	Male C57BL/6J mice	CUMS comorbid dry eye	5 and 10 mg/kg, p.o.	6 weeks	Sucrose preference of SPT ↑, immobility time of TST and FST ↓, corneal damage↓, and tear secretion ↑	IL-1β ↓, TNF-α↓, IL-6 ↓, IL-18 ↓, Sirt1 protein ↑, Ac-NF-κB ↓, GSDMD-N/GSDMD ↓, NLRP3 ↓, and cleaved-caspase1/caspase1 protein ↓ (Serum and HIP)	Anti-neuroinflammatory, inhibit microglial activation, and anti-apoptosis	[18]
In vivo/*vitro*	Newborn SD rats and male ICR mice; primary hippocampal neurons	CUMS and estrogen-deficient model	10, 20, and 40 mg/kg, i.p.; 0.1, 1, or 10 μM	2 weeks; 48 h	Immobility time of FST↓ and time spent and frequency upright behavior of OFT ↑	PMAT gene expression ↑ and 5-HT re-uptake ↓ (HIP)	Inhibit monoamine transporters	[44]
In vitro	SH-SY5Y cells	–	0.1, 1, 10, 50, and 100 μM	24 h	–	Cell viability ↓ and MAO-A activity ↓ (SH-SY5Y cells)	Inhibit the metabolism of 5-HT	[45]
In vivo/*vitro*	Male ICR mice; HEK-293 cells transfected with human NE transporter	–	5, 10 mg/kg, i.p.; 10 or 30 μg/mL	–	Immobile behavior of FST ↓	Intracellular NE uptake and c-aminobutyric acid-mediated Cl- influx ↑ (Human neuroblastoma cells)	Anti-oxidative stress	[49]
In vivo	Male Kunming mice	Noise-stress	20 and 60 mg/kg, p.o.	3 weeks	Sucrose preference of SPT ↑, the locomotor activity ↑, and immobility time of TST and FST ↓	IL-1β ↓, TNF-α ↓, IL-6 ↓, BDNF ↑, P − mTOR ↑, 5-HT ↑, NE ↑, SYN ↑, and PSD-95 ↑	Anti-neuroinflammatory and improve the dendritic deficits	[55]
In vivo	Male Wistar rats	CUMS	25 mg/kg, p.o.	6 weeks	Sucrose preference of SPT ↑, immobility time ↓, and memory and cognition ↑	EFNA5 ↑, EPHB4 ↑, EPHA4 ↑, SEMA7A ↑, NTNG1 ↑, UNC5B ↑, DCC ↑, and L1CAM ↑ (CSF)	Improve synaptic function	[56]
In vivo	Male Wistar rats	Cobalt chloride	100 mg/kg, p.o.	7 days	Motor coordination of forelimb ↑, spatial learning and memory ↑, and exploration and locomotion ↑	NO ↓, MDA ↓, H_2O_2 ↓, SOD and GST activities ↑, GFAP+ cells ↓, and AchE activity ↓ (Serum, cortex)	Protect synaptic function, antioxidation, and anti-inflammation	[57]
In vivo	Adult male Wister rats	CCI	10, 25, and 50 mg/kg, i.p.	21 days	Pain threshold ↑, pain sensitivity ↓, allodynia scores ↓, swimming time ↑, climbing time ↑, and immobility time ↓	Catalase ↑, SOD ↑, MDA ↓, BDNF ↑, GDNF ↑, Nrf2 ↑, NF-κB ↓, NLRP3 ↓, IL-1β ↓, IL-18 ↓, IL-6 ↓, and TNF-α ↓ (HIP and PFC)	Anti-oxidative stress, anti-apoptosis, and anti-neuroinflammation	[63]
In vivo	Male C57BL/6 mice	LPS	25 and 50 mg/kg, p.o.	3 days	Sucrose preference of SPT ↑, and immobility time of FST ↓	IL-6 ↓, IL-1β↓, NLRP3↓, TRAF6 ↓, A20 ↑, Nrf2 ↑, and NF-κB ↓ (HIP and PFC)	Anti-neuroinflammatory	[69]
In vivo/*vitro*	Adult male ICR mice; SH-SY5Y Cells; Human Neural Stem Cells	LPS	10 mg/kg, p.o.; 1 μM	8 days; 24 h	Immobility time of FST ↓	Cell viability ↑, $GFAP^+$ cells ↑, expression of BMP2 and STAT3 ↑, differentiation of hNSCs into astrocytes ↑, IL-6↓, TNF-α ↓, mature BDNF ↑, dopamine ↑, and noradrenaline↑ (hypothalamus and cerebral cortex)	Promote astrogliogenesis, anti-inflammation	[70]
In vivo	APP23 mice	AD	20 mg/kg, i.p.	29 weeks	Global activity in TST ↑, and immobility time of FST ↓	Aβ ↓, IL-1β ↓, eIF2a phosphorylation ↓, and PS1C ↓ (HIP)	Suppress ER stress, inhibit microglial activation	[71]
In vivo/*vitro*	Female BALB/c mice Hippocampal neuron cell line (HT-22)	BCRD	50 mg/kg, i.p.; 20 μM	21 days; 24 h	Interest in exploring new environments ↑, and static time of TST and FST ↓	TUNEL+ cells ↓, caspase-1+ neurons ↓, NLRP3 ↓, caspase-1 ↓, GSDMD-N ↓, IL-1β↓, IL-18 ↓, TRAF6 ↓, miR-124-3p ↑, p-NF-κB ↓, and p-IκB ↓ (HIP)	Anti-pyroptosis	[79]
In vivo	129Sv/Ev male mice	CORT	1, 3, and 10 mg/kg, i.p.	2 weeks	Time spent in the center of OFT ↑, number of crossings ↑, and immobility time of FST ↓	BrdU+ cells ↑, DCX+ cells ↑, mature BDNF ↑, Bax ↓, and Bcl-2 ↑ (HIP)	Regulate endocannabinoid system and anti-apoptosis	[80]

(*continued on next page*)

Table 3 (*continued*)

In vivo/vitro	Strains/cell lines	Models	Doses and administration	Duration	Behavioral evaluation	Molecular changes (Tissue/Cells)	Pharmacological effects	Refs.
In vivo	Aging male Wistar rats	CUMS	25 mg/kg, p.o.	6 weeks	Sucrose preference of SPT ↑, central region distance and time ratio of OFT ↑, immobility time of FST ↓, and time and distance ratios of MWM ↑	PS, PC and PE in the hippocampus ↑, hippocampal LC3II ↑, and p62 ↓ (HIP and PFC)	Regulate glycerophospholipid metabolic and anti-autophagy	[81]
In vivo/*vitro*	Male ICR mice; SH-SY5Y cells	CORT, tunicamycin	50 mg/kg, p.o.; 0.1−10 μM	23 days; 1 h	Immobility time of FST and tail suspension test ↓	GRP78 and GRP94 expression *in vitro* ↑/*in vivo* ↓, and cleaved caspase-3 ↓ (HIP)	Inhibition of ER stress and antioxidant activity	[88]
In vivo/*vitro*	Male Wistar rats. Hippocampal NSCs, CPECs	LOD	25 mg/kg, p.o.; 20 μM	6 weeks; 72 h	Sucrose preference of SPT ↑, locomotion activity in OFT ↑, accuracy of MWM ↑, and immobility time ↓	Viability of NSCs ↑, ZO-1 ↑, PCFT ↑, RFC ↑, FR-α ↑, and 5-MTHF ↑ (plasma, CSF, and HIP)	Enhance the folate brain transport	[92]
In vivo	Male Sprague −Dawley rats	PTSD	10 and 20 mg/kg, i.p.	14 days	Freezing response of FCT ↓, immobility time of FST ↓, percentage of time spent, and number of entries, and the open arms of EPM ↑	CORT ↓, 5-HT ↑, NE ↓, and the glucocorticoid and mineralocorticoid mRNA ↑ (HIP and PFC)	Regulation of the HPA axis and monoamine balance	[115]

−: no data. CCI: chronic constriction injury; i.p.: intraperitoneal injections; SOD: superoxide dismutase; MDA: malondialdehyde; BDNF: brain-derived neurotrophic factor; GDNF: glial cell derived neurotrophic factor; Nrf2: nuclear factor-E2 p45-related factor 2; NF-κB: nuclear factor kappa B; NLRP3: nod-like receptor family pyrin domain containing 3; IL: interleukin; TNF: tumor necrosis factor; HIP: hippocampus; PFC: prefrontal cortex; ICR: Institute of Cancer Research; HEK-293: human embryonic kidney 293; NE: norepinephrine; FST: forced swimming test; LPS: lipopolysaccharide; p.o.: per os; SPT: sucrose preference test; TRAF6: tumor necrosis factor receptor associated factor 6; A20: zinc finger protein A20; SD rat: Sprague Dawley rat; CUMS: chronic unpredictable mild stress; OFT, open field test; PMAT: plasma membrane monoamine transporter; 5-HT: 5-hydroxytryptamine; AD: Alzheimer's disease; TST: tail suspension test; Aβ: amyloid β-protein; eIF2a: eukaryotic translation initiation factor 2 subunit alpha; PS1C: C-terminal fragment of presenilin-1; ER: endoplasmic reticulum; Sirt1: silencing information modulator related enzyme 1; GSDMD: gasdermin-D; mTOR: mammalian target of rapamycin; SYN: synapse; PSD-95: postsynaptic density protein 95; MWM: morris water maze; PS: phosphatidylserine; PC: phosphatidylcholine; PE: phosphatidylethanolamine; LC3: microtubule associated protein 1 light chain 3; PTSD: post-traumatic stress disorder; FCT: fear conditioning test; EPM: elevated plus maze; CORT: corticosterone; HPA: the hypothalamic−pituitary−adrenal axis; SH-SY5Y: human neuroblastoma cell line SK-N-SH; GFAP: glial fibrillary acidic protein; BMP2: bone morphogenetic protein 2; STAT3: signal transducer and activator of transcription; hNSCs: human neural stem cells; CORT: corticosterone; BrdU: bromodeoxyuridine; DCX: doublecortin; Bax: B-cell lymphoma-2 associated X protein; Bcl-2: B-cell lymphoma-2; BALB/c: Bagg albino mice; BCRD: breast cancer-related depression; TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labeling; miR: microRNA; IκB: IkappaB; NSCs: neural stem cells; CPECs: choroid plexus epithelial cells; LOD: late-onset depression; ZO-1: zona occludens protein 1; PCFT: proton-coupled folate transporter; RFC: reduced folate carrier; FR-α: folate receptor alpha; 5-MTHF: 5-methyltetrahydrofolate; CSF: cerebrospinal fluid; EFNA5: ephrin A5; EPHB4: ephrin type-B receptor 4; EPHA4: ephrin type-A receptor 4; SEMA7A: semaphorin 7A; NTNG1: netrin G1; UNC5B: netrin receptor UNC5B; DCC: netrin receptor DCC; L1CAM: neural cell adhesion molecule L1; GRP78: 78 kDa glucose-regulated protein; GRP94: 94 kDa glucose-regulated protein; MAO-A: monoamine oxidase type A; NO: nitric oxide; H_2O_2: hydrogen peroxide; GST: glutathione S-transferase; GFAP: glial fibrillary acidic protein; AChE: acetylcholinesterase.

Table 4
Binding energy of molecular docking.

Serial number	Target	Corresponding species	PDB ID	Binding energy (kcal/mol)	Binding energy (kJ/mol)	Hydrogen bonding
1	AKT1	Mankind	1UNQ	−4.87	−20.3897	+
2	ESR1	Mankind	1A52	−4.49	−18.7987	+
3	PTGS2	Mankind	5F19	−4.91	−20.5571	+
4	IGF1R	Mankind	1IGR	−4.66	−19.5105	+
5	EGFR	Mankind	1M14	−4.24	−17.7520	+

AKT1: serine/threonine kinase 1; ESR1: estrogen receptor 1; PTGS2: prostaglandin endoperoxide synthase 2; ICF1R: insulin-like growth factor 1; EGFR: epidermal growth factor receptor.

research lacks investigation into the bioavailability of luteolin within the brain.

7.2. Toxicity

As a dietary phytochemical, luteolin has very low toxicity. De Leo et al. [151] reported that luteolin showed a good level of safety in larval zebrafish. Studies have shown that the median lethal dose (LD_{50}) of luteolin injected intraperitoneally into mice is 180 mg/kg. Luteolin showed no significant effect on the general activities, liver and kidney function, hemogram, or important organs of guinea pigs after 20 days of gavage, of guinea pigs with 50 times of luteolin [152]. The LD of luteolin administered to mice by intraperitoneal and intramuscular injection was also reported as 411.5 ± 79.3 mg/kg and 592 ± 55.6 mg/kg, respectively [153]. Xiong et al. [154] found that the LD_{50} of luteolin was 460 mg/kg, and in rats, the LD_{50} of luteolin was 411 mg/kg intraperitoneally and 5000 mg/kg orally. Additionally, luteolin administered intraperitoneally at a dose of 100 mg/kg did not cause significant liver or kidney toxicity in male mice, indicating a good safety profile. Furthermore, luteolin and its analogues may have adverse effects on the endocrine system of mammals, which may be related to the estrogenic activity of luteolin and its antagonistic effect on progesterone receptors [155]. Since the oral absorption rate of luteolin is 15%, dietary supplements are unlikely to reach concentrations that could induce toxicity [156]. However, whether it is safe for use in humans remains unclear and requires further evaluation in clinical trials.

8. Perspective and limitations of luteolin as antidepressant agents

Luteolin, a natural flavonoid, has garnered attention for its potential therapeutic roles in complementary and alternative medicine. With antioxidant properties, luteolin may mitigate oxidative stress, offering protection against oxidant-related diseases including cardiovascular and cancerous conditions [157]. Additionally, its neuroprotective capabilities are under investigation for the potential treatment of neurodegenerative disorders such as Alzheimer's, Parkinson's disease, and stroke, by shielding brain cells from injury [158−160]. Luteolin is also considered to possess anti-inflammatory attributes, which may be beneficial in the management of inflammatory diseases like arthritis and inflammatory bowel syndrome [161]. Furthermore, research indicates that luteolin could contribute to the prevention and treatment of certain cancers by inhibiting tumor proliferation and promoting apoptosis [153]. Lastly, evidence suggests that luteolin may enhance insulin sensitivity and glycemic control, holding potential benefits for individuals with diabetes [162].

Some studies indicate that luteolin may have antidepressant properties, which could be useful in the treatment of depression. Seventeen pre-clinical studies were included in this systematic review. Combined with the results of these studies, luteolin, luteolin-containing herbs, and compound preparations of Chinese medicine have shown neuroprotective and antidepressant potentials in both *in vitro* and *in vivo* models. Luteolin promotes intracellular NE uptake, inhibits 5-HT reuptake, up-regulates the expression of SYN, PSD-95, BDNF, Bcl-2, SOD, and GST, and decreases the expression of MDA, caspase-3 and Aβ, thus exerting an antidepressant effect. The antidepressant effects of luteolin are mediated through multiple mechanisms, including anti-OS, anti-apoptosis, anti-inflammation, anti-ERS, dopamine transport, neurosynaptic protection, HPA axis regulation, and 5-HT metabolism. Additionally, we combined network pharmacology and molecular docking to identify multiple pathways and potential targets of luteolin as an antidepressant. These pathways include endocrine resistance, estrogen signaling, EGFR tyrosine kinase inhibitor resistance, and the HIF-1 signaling pathway. The potential targets identified in the network analysis were IGF1R, AKT1, PTGS2, ESR1, and EGFR, and luteolin showed ideal affinity for these targets. These studies suggest that luteolin exerts its positive effects on depression via multiple targets, pathways, and mechanisms.

Although luteolin has been shown to have antidepressant and neuroprotective effects in several *in vitro* and *in vivo* depression models, the doses of luteolin used in different studies ranged from 1.0 to 100 mg/kg, which may cause bias in the results. Therefore, further exploration is warranted to determine the optimal luteolin dosage and intervention time to meet different experimental requirements. However, the mechanisms underlying the antidepressant effects of luteolin remain unclear. In different models of depression, luteolin has been shown to exert antidepressant effects through a variety of mechanisms. Exploring the primary antidepressant mechanisms of luteolin will facilitate its early use in clinical practice. In addition, the antidepressant efficacy and potential mechanisms of action of Chinese herbal preparations containing luteolin remain unclear. Therefore, the scope of research should be expanded to investigate the effects of different components of compound preparations on luteolin and the interactions between different components to provide an experimental basis for the antidepressant treatment using Chinese herbal preparations.

It is noteworthy that although luteolin has shown promise in preclinical and clinical studies for the treatment of depression, its poor water-lipid solubility and low bioavailability significantly limit its clinical application. Studies have shown that the oral absorption rate of 100 mg/kg luteolin in rats is only 10% and the maximum plasma concentration of luteolin is only 3.79 μg/mL. However, the clearance rate of luteolin in the plasma is high, and it is difficult to achieve an effective plasma concentration by oral and intravenous injection [146]. Therefore, improving the bioavailability and targeting of luteolin, thereby enhancing its efficacy, is important for promoting its early clinical application. Fortunately, numerous studies on particle drug delivery systems, solid dispersion technology, phospholipid complexes, inclusion technologies, hydrogels, and multi-technology applications for different therapeutic targets have played a role in promoting absorption and improving bioavailability. Compared to the original drug, bioavailability was significantly improved, providing a valuable basis for subsequent research. Furthermore, many cutting-edge drug delivery ideas have emerged in extant preparation research, such as the application of a

variety of new carriers, block polymers, modified polymers, three-dimensional network hydrogel delivery systems, and various drug delivery methods. New surfactants, protein carriers, temperature- and pH-sensitive polymer materials, biomimetic carriers, and self-assembling nanotechnology inject vitality and application prospects into the preparation of luteolin.

9. Conclusion

In conclusion, exploring the mechanism of action of luteolin as an antidepressant from a targeted perspective is a direction for future research. Luteolin, luteolin-containing herbs, and Chinese herbal preparations containing luteolin may be used as important ingredients in the treatment of depression. However, further studies on the antidepressant mechanism of luteolin and development of its pharmacological preparations to improve its bioavailability are required to overcome these major difficulties. Multicenter randomized controlled trials are needed to confirm the antidepressant efficacy of luteolin.

CRediT authorship contribution statement

Jiayu Zhou: Writing – original draft. **Ziyi Wu:** Methodology, Investigation, Data curation. **Ping Zhao:** Writing – review & editing, Validation, Supervision.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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