Contents lists available at ScienceDirect

Digital Chinese Medicine

journal homepage: http://www.keaipublishing.com/dcmed

Antidepressant-like active ingredients and their related mechanisms of functional foods or medicine and food homologous products

YE Tian[a], XU Mengtao[a], FANG Jingpeng[a], WU Qinxuan[b], ZOU Xiaoyan[b], YAN Fangqin[c], QING Zhixing[a*]

a. Hunan Key Laboratory of Traditional Chinese Veterinary Medicine, Hunan Agricultural University, Changsha, Hunan 410128, China
b. College of Pharmacy, Changsha Medical University, Changsha, Hunan 410219, China
c. College of Chemistry, Zhengzhou University, Zhengzhou, Henan 450001, China

A R T I C L E I N F O

Article history
Received 03 January 2023
Accepted 20 February 2023
Available online 25 March 2023

Keywords
Antidepressant
Medicine and food homologous
Functional food
Extract
Active ingredients
Traditional Chinese medicine (TCM)

A B S T R A C T

Objective To provide a new idea for the treatment of depression by summarizing the antidepressant effect and mechanism of active ingredients in functional food, and medicine and food homologous products.

Methods The literature related to the antidepressant of functional food or medicine and food homologous products from September 25, 1996 to September 5, 2022 was collected through PubMed, Google Academic, Web of Science, and China National Knowledge Infrastructure (CNKI) databases. After that, their antidepressant active ingredients and mechanism of action were systematically summarized and analyzed.

Results A total of 146 pieces of literature were involved in the study, including 67 plant-derived functional foods or medicine and food homologous products, 32 antidepressant extracts (including 8 flavonoid extracts), and 87 antidepressant active ingredients. The 87 antidepressant active ingredients include 7 terpenes, 22 saponins, 15 flavonoids, 11 phenylpropanoids, 7 phenols, 6 sugars, 8 alkaloids, and 11 others.

Conclusion The study summarized and analyzed the active ingredients and mechanisms of antidepressants in functional foods and medicine and food homologous products, which provides a new vision for the development of new antidepressants and a potential alternative treatment for patients with depression.

1 Introduction

Depression is a common mental disorder in modern society. In general, patients with depression are hampered by emotional symptoms such as depression, loss of self-confidence, pessimism, and lack of interest, as well as physical symptoms like sleep disorder and lack of appetite, which pose great threat to their quality of life [1]. Following the World Health Organization (WHO) report, there are more than 350 million depression patients worldwide, accounting for 4.4% of the world population [2]. Depression is the most prominent factor leading to individual disability, and 7.5% of the disability in the world is related to depression [2]. According to the 2019 mental health survey, the lifetime prevalence of adult depression in China is 6.8%, and the number of people suffering from depression is as high as 95 million [3]. With the sudden outbreak of the Corona Virus Disease 2019 (COVID-19)

*Corresponding author: QING Zhixing, E-mail: qingzhixing@hunau.edu.cn.

Peer review under the responsibility of Hunan University of Chinese Medicine.

DOI: 10.1016/j.dcmed.2023.02.001
Citation: YE T, XU MT, FANG JP, et al. Antidepressant-like active ingredients and their related mechanisms of functional foods or medicine and food homologous products. Digital Chinese Medicine, 2023, 6(1): 9-27.

pandemic and the tightening prevention-control measures, the global population was immersed in a state of extreme tension and thus a higher risk of depression [4]. Vulnerable populations and health professionals are particularly affected by the impact of the pandemic on mental health [5, 6]. It was reported that, in 2020 alone, the global cases of severe depression increased by 27.6% [7], and the prevalence of depressive symptoms did not alleviate with the control over the epidemic [8]. At present, depression has become the second largest disease burden in China, ranking first among various mental and psychological diseases [8, 9].

Current mainstream treatments for depressive disorders include psychotherapy, electroconvulsive therapy, and drug therapy [10]. Among the three options, psychotherapies like cognitive behavioral therapy (CBT) and interpersonal therapy (IPT) are generally considered the initial treatment for mild to moderate major depression [10], while electroconvulsive therapy, which involves producing generalized seizures using electrical stimulation, is regarded as a final resort in cases where medication and psychotherapy have failed [11]. In contrast, drug therapy is the most extensively applied treatment. Among various antidepressant drugs, selective serotonin reuptake inhibitors (SSRIs), relatively superior to other traditional tricyclic antidepressants in safety [12], has occupied the dominant position in market. Still, it can lead to many adverse reactions, including gastrointestinal bleeding, hepatotoxicity, metabolic disturbances, weight gain, sexual dysfunction, and discontinuation syndromes [13-15]. A study has shown that up to 43% of major depressive disorder (MDD) patients may discontinue antidepressants on account of adverse reactions during treatment [16]. The therapeutic effects are not necessarily guaranteed, and meta-analyses indicated that these existing drugs were only effective in less than half of patients with depression [17, 18]; even under the treatment of Citalopram, a representative drug, symptoms cannot be completely eliminated for 70% of patients [19]. The disadvantages of low cure rates and high prices make it increasingly urgent to develop new, fast-acting, mild, and inexpensive therapeutic drugs.

In recent years, a large number of studies have focused on natural products including functional foods or medicine and food homologous plants, which display significant antidepressant activity and low side effects [20, 21]. Those plant-derived medicines and foods contain a wide variety of natural compounds with antidepressant activity, including terpenes, saponins, flavonoids, phenylpropanoids, phenols, carbohydrates, and alkaloids. These compounds exert antidepressant effect through different mechanisms, such as affecting the expression of neurotransmitters and their receptors, regulating the hypothalamic-pituitary-adrenal (HPA) axis as well as modulating neuronal plasticity and related signaling pathways [22]. However, there are barely any articles to review the progress in this field. Therefore, this paper summarized the antidepressant effects of 32 extracts (including 8 flavonoid extracts) of medicine and food homologous products, 87 active components, as well as their related mechanisms as they were reported in the last 30 years, which lays the foundation for the development of new antidepressant functional foods or antidepressant drugs. Part of the representative medicine and food homologous plants and compounds are shown in Figure 1.

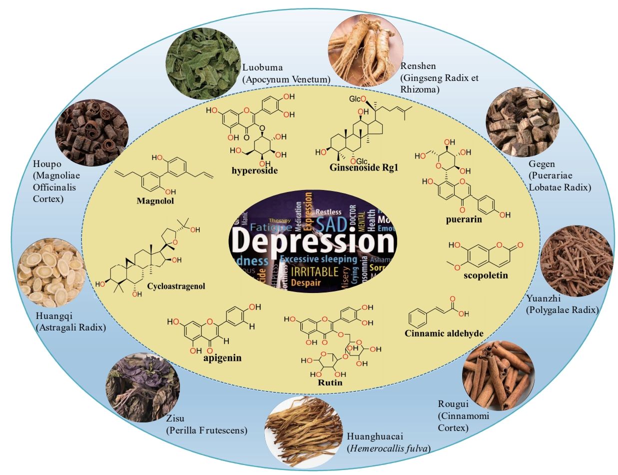

Figure 1 The representative functional foods or medicine and food homologous products with antidepressant activity and their active components

2 Data and methods

All the available information presented in this review concerning functional foods or medicine and food homologous products with antidepressant effect was gathered from academic databases, including PubMed, Google Scholar, Web of Science, and China National Knowledge Infrastructure (CNKI), from September 25, 1996 to September 5, 2022. In addition, part of the information was obtained from local books, patents, and doctoral and master's dissertations. The keywords of "antidepressant" in the title, and "plant" "extract" "herb" and "active ingredients" in the whole text were used for online search. The structures of the antidepressant activity component, which were mentioned in the articles, were obtained from theses, books, databases, and other reliable sources. The articles with unclear experimental results, unreasonable research design or those neglecting the mechanisms of action were excluded. A summary of main findings is represented in Figure 2.

3 Results

Many studies concentrate on the antidepressant activity of the extracts or monomeric compounds isolated from the medicine and food homologous products. Extracts

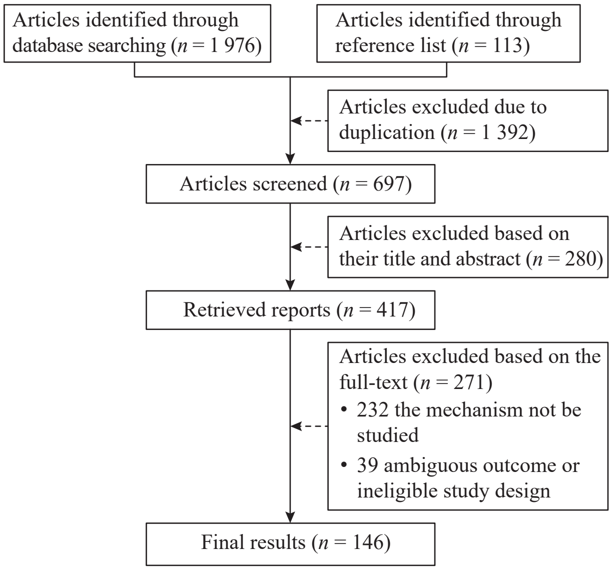

Figure 2 Flowchart of screening and selection of eligible articles

comprise ethanol extract, water extract, and organic solvent extract; monomer active ingredients consist of terpenoids, saponins, flavonoids, phenylpropanoids, phenols, alkaloids, and sugars. The top five medicine and food homological plant extracts with anti-depressive activity reported in the literature are shown in Figure 3.

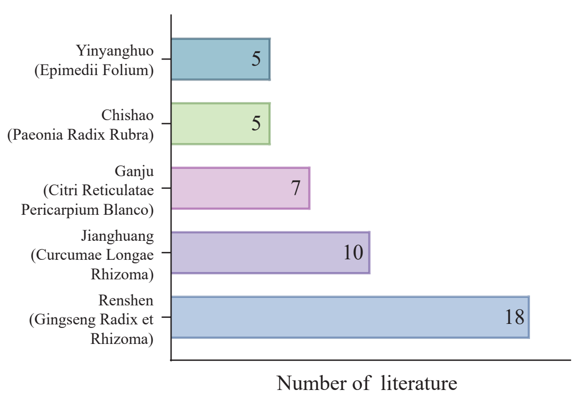

Figure 3 The top five medicine and food homologous product extracts with anti-depressive activity reported in the literature

3.1 Extracts with antidepressant activity

The ethanol extracts (YZ-30% and YZ-50%), obtained from Yuanzhi (Polygalae Radix) by conventional ethanol extraction, displayed significant antidepressant activity by reducing the immobility time of depressed mice in the forced swimming test (FST) and tail suspension test (TST). The potential mechanism was blocking the reuptake of monoamine neurotransmitters [20]. The ethanol extract of Tianma (Gastrodiae Rhizoma) could increase monoamine neurotransmitter concentrations in the hippocampus and striatum of mice and exhibits significant antidepressant activity [23]. Lianzi (Nelumbinis Semen) ethanol extract also exerted antidepressant effect by regulating depression-related neurotransmitter levels [24]. The antidepressant activity of ethanol extracts of Yuanzhi (Polygalae Radix), Tianma (Gastrodiae Rhizoma) and Lianzi (Nelumbinis Semen) are all related to increasing the neurotransmitters. The ethanol extract of Gegen (Puerariae Lobatae Radix) could reverse the decline of norepinephrine (NE) and dihydroxyphenylacetic acid (DOPAC) in depressed mice [25]. The ethanol extract of Jiaogulan (Gynostemma Pentaphyllum) could dramatically shorten the immobility time of depressed mice in TST and FST, and the antidepressant activity of the extract was the same as the positive drug named fluoxetine hydrochloride [26]. Other antidepressant-like extracts from medicine and food homologous products and the related mechanisms are shown in Table 1.

3.2 Terpenoids

Paeoniflorin (**1**) and albiflorin (**2**), two bicyclic monoterpene compounds isolated from Chishao (Paeonia Radix Rubra), displayed significant antidepressant effects. The former is related to its functions in the up-regulation of the monoaminergic neurotransmitters and brain-derived neurotrophic factor (BDNF) levels, inhibition of the HPA axis hyperfunction, promotion of hippocampus neurogenesis, alleviation of inflammatory reaction, and regulation of extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathway [45-48]. The latter exerts antidepressant effect by modulating the metabolism of amino acids and regulating gut microbes [49]. Eryngiolide A (**3**), isolated from Xingbaogu (Pleurotus Eryngii), showed notable antidepressant activity at 0.2, 1, and 5 mg/kg by reducing the immobility time of depressed mice in FST and TST [50]. Genipin (**4**) identified from Zhizi (Gardeniae Fructus) exhibited significant antidepressant activity by increasing the contents of NE and 5-HT in the brain of depressed mice [51]. Asiaticoside (**5**), asiatic acid (**6**), and madecassic acid (**7**) isolated from Jixuecao (Centella Herba), which can be eaten raw and used as an ingredient in herbal tea, have remarkable antidepressant effects and dramatically reduce the immobility time of depressed mice in FST and TST [50, 52]. The structures of terpenoid compounds **1**-**7** with significant antidepressant activity are shown in Figure 4.

3.3 Saponins

3.3.1 Total saponins Total saponins extracted from Baihe (Lilium lancifolium Thunb), Sanqi (Panax Notoginseng), Chishao (Paeoniae Radix Rubra), and Jili (Tribulus Terrestris) displayed antidepressant activity. The immobility time of depressed mice in FST and TST was significantly shortened by medium and low doses of total brownioside [53]. Notoginsenoside could alleviate

Table 1 The medicine and food homologous product extracts with significant antidepressant activity

Source	Effective component	Antidepressant activity/Mechanism	Reference
Ethanol extract			
Yuanzhi (Polygalae Radix)	Saponosides	Blocking the reuptake of monoamine neurotransmitters	[20]
Tianma (Gastrodiae Rhizoma)	/	Increasing monoamine neurotransmitter levels in hippocampus and striatum of depressed mice	[23]
Lianzi (Nelumbinis Semen)	Isoquercetin	Regulating neurotransmitter levels	[24]
Gegen (Puerariae Lobatae Radix)	Flavonoids, Coumarins	Reversing the decline of NE and DOPAC in depressed mice	[25]
Jiaogulan (Gynostemma Pentaphyllum)	/	Significantly decreasing the immobility time of depressed mice in TST and FST	[26]
Hongjingtian (Rhodiolae Crenulatae Radix et Rhizoma)	Rhodioloside B and C	Inhibition of monoamine oxidase activity	[27]
Jiegeng (Platycodon Grandiflorus)	Asruin, Delphinidin, Dihydroquercetin, Luteolin7-*O*-glucopyranoside	Regulation of glycerophospholipid and linoleic acid metabolism pathways	[28]
Luobuma (Apocynum Venetum)	Hyperoside and quercitrin	Significantly decreasing the immobility time of depressed mice in FST	[29]
Bajitian (Morindae Officinalis Radix)	Nystose, Lnulin-typepentasaccharide	Regulating neurotransmitter dopamine (DA)	[30]
Zhima (Sesamum Indicum)	Sesamol	Increasing the level of 5-hydroxytryptamine (5-HT) in hippocampus of depressed mice	[31]
Rougui (Cinnamomum Cassiapresl)	/	Inhibiting the inflammatory factor in the hippocampus of depressed mice	[32]
Xueju (Coreopsistinctoria)	Polyphenols	Reinforcement of 5-HT and activation of NE level	[20]
Jicai (Capsella Bursa-Pastoris)	Butyl formate, 2-methoxy-4-vinyl phenol, Methyl isoeugenol 1,3-isopropoxy-5-ethyl phenol	Regulating hormones, neurotransmitters, and BDNF expression in brain of depressed mice	[33]
Aqueous extract			
Hongjingtian (Rhodiolae Crenulatae Radix et Rhizoma)	Rosiridin	Inhibition of monoamine oxidase activity	[27]
Jianghuang (Curcumae Longae Rhizoma Rhizoma)	Curcumin	Inhibition of monoamine oxidase A (MAO-A) enzyme activity of depressed mice	[34]
Heshouwu (Polygoni Multiflori Radix)	/	Significantly shortening the immobility time of depressed mice in TST and FST	[35]
Wuweizi (Schisandra Chinensis)	/	Activation of JAK1/STAT3 signaling pathway to protect hippocampal neurons	[36]
Jinhuachaye (Camellia Chrysantha Tuyama)	Quercetin, Rutin, Caffeine, L-theanine, Ginsenoside Rgl	Blocking mitochondrial apoptotic signaling pathway, inhibiting corticosterone-induced apoptosis, and upregulating BDNF gene expression by activating PKA-CREB signaling pathway	[37]
Qiukui (Abelmoschus Esculentus)	/	Increasing the levels of monoamine neurotransmitters Ach and GABA in the brain, inhibiting the excessive excitation of HPA axis, and protecting brain cells	[38]
Luofumu (Rauwolfia Vomitoria)	/	Inhibition of monoamine oxidase activity	[39]
Tiandong (Asparagi Radix)	Shatavrins	Regulating the BDNF-TrkB pathway	[40]
Other extractions			
Duzhong (Eucommia Ulmoides)	/	Relieving depression of mice	[41]
Maka (Lepidium Meyenii)	Linoleic aid	Inhibiting the increase of serum corticosterone (CORT) secretion, and increasing DA and NE levels and decreasing ROS activity in the depressed mice brain	[42]
Ningmeng (Citrus Limon)	/	Regulation of DA and 5-HT	[43]
Kekedou (Theobroma Cacao Bean)	Flavonoids, Glycosides, Procyanidins, Catechins	Significantly shortening the immobility time of depressed mice in FST	[44]

depressive symptoms by modulating the concentration of monoamine neurotransmitters in the brain of depressed mice, as well as regulating the level of cyclic adenosine monophosphate (cAMP), protein kinase A (PKA), and BDNF in depressed mice [54, 55]. The antidepressant activity of total saponins of Chishao (Paeoniae Radix Rubra) is related to regulating monoamine neurotransmitters such as NA, 5-HT and their receptors in different regions of the brain [56]. The antidepressant mechanism of Jili (Tribulus Terrestris) saponin is to increase the content of monoamine neurotransmitters such as 5-HT and γ-aminobutyric acid (GABA) in blood, and regulate the expression of specific genes in the hippocampus [57].

3.3.2 Monomer saponins The antidepressant effect of Renshen (Gingseng Radix et Rhizoma), a common medicinal and edible food that has always been regarded as the king of herbs, has become a research hotspot in recent years (Figure 3). The antidepressant active ingredients of Renshen (Gingseng Radix et Rhizoma) have been widely studied, and it is shown that ginsenoside Rg1 (**8**) shows significant antidepressant activity by regulating glucocorticoid receptor (GR) expression, amino acid, and BDNF levels, as well as improving synaptic ultrastructure in prefrontal cortex [58-61]. Recent studies have found that it can upregulate Cx43 expression and protect astrocyte gap junctions within the prefrontal cortex in animal models of depression [62-64]. The antidepressant mechanism of ginsenoside Rb1 (**9**) may be related to regulating brain-derived neurotrophic factor/TrkBtyrosine kinase receptor (BDNF/TrkB) signaling pathway and AKT pathway, suppressing inflammation, and modulating the HPA axis [65-67]. In addition, other saponins isolated and identified from Renshen (Gingseng Radix et Rhizoma), such as ginsenoside Rh2 (**10**) [68], ginsenoside Rg2 (**11**) [69], ginsenoside Rg3 (**12**) [70], ginsenoside Rb3 (**13**) [71], ginsenoside Re (**14**) [72], ginsenoside Rd (**15**) [73], and ginsenoside **16-23** [50, 74] have significant antidepressant activity. The above data indicate that Renshen (Gingseng Radix et Rhizoma) extract and its saponins are essential plant-derived candidates for developing new antidepressants.

Two saponins, cyprotusides A (**24**) and cyprotusides B (**25**), isolated from Xiangfu (Cyperi Rhizoma), displayed significant antidepressant effect [75]. Anemarrhena asphodeloides B-II (**26**), B-III (**27**), and Anemarrhena asphodeloides saponin (**28**) can be obtained from Zhimu (Anemarrhenae Rhizoma). Compound **26** exerts antidepressant activity by inhibition of monoamine oxidase activity as well as elevation of 5-HT in the nervous system and DA in the brain [76]; compound **27** shows antidepressant activity via the regulation of inflammatory cytokines, the BNDF signaling pathway, and synaptic plasticity-related proteins [77]; the antidepressant mechanism of compound **28** is linked to increasing the 5-HT and NE levels in the hypothalamus and the hippocampus, and inhibiting monoamine oxidase type A and B activity [78]. Glycyrrhizic acid (**29**) is a triterpenoid saponin derived from Gancao (Glycyrrhizae Radix et Rhizoma), and its antidepressant effect has been found to be related to ameliorating the kynurenine pathway [79]. The structures of saponins **8-29** with antidepressant activity identified from the traditional medicine and food homologous products are shown in Figure 5.

3.4 Flavonoids

3.4.1 Total flavonoids In recent years, the research on the antidepressant effect, structure-activity relationship, and related mechanism of flavonoids has been dramatically developed. A large number of studies have reported that the total flavonoids extracted from Gancao (Glycyrrhizae Radix et Rhizoma) , Suanzaoren (Ziziphi spinosae Semen), Xuancao (Hemerocallis Fulva), Yuxingcao (Houttuyniae Herba) and other functional foods or

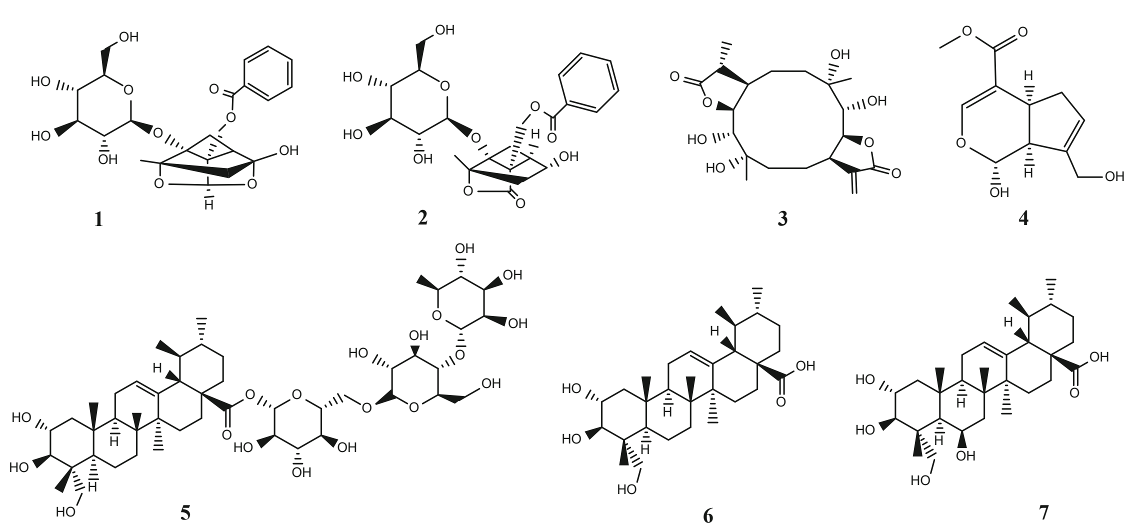

Figure 4 The structures of terpenoids **1-7**

(**1**) Paeoniflorin; (**2**) Albiflorin; (**3**) Eryngiolide A; (**4**) Genipin; (**5**) Asiaticoside; (**6**) Asiatic acid; (**7**) Hydroxyl asiatic acid.

medicine and food homologous products have significant antidepressant activity. Total flavonoids extracts from antidepressant food and medicine products are shown in Table 2.

3.4.2 Flavonoids and dihydroflavonoids Takahiro and other scholars have attributed the antidepressant activity of perilla to Apigenin (**30**), a flavonoid compound widely distributed in nature, which could regulate the level of DA [89]. It also exists extensively in Ganju (Citri Reticulatae Pericarpium Blanco) and displays significant antidepressant activity by increasing the concentration of 5-HT in the brain of rats with chronic mild stress (CMS), and reducing the concentration of serotonin metabolites (5-hydroxyindoleacetic acid, 5-HIAA), DA, and the ratio of 5-HIAA/5-HT, inhibiting interleukin (IL)-1β

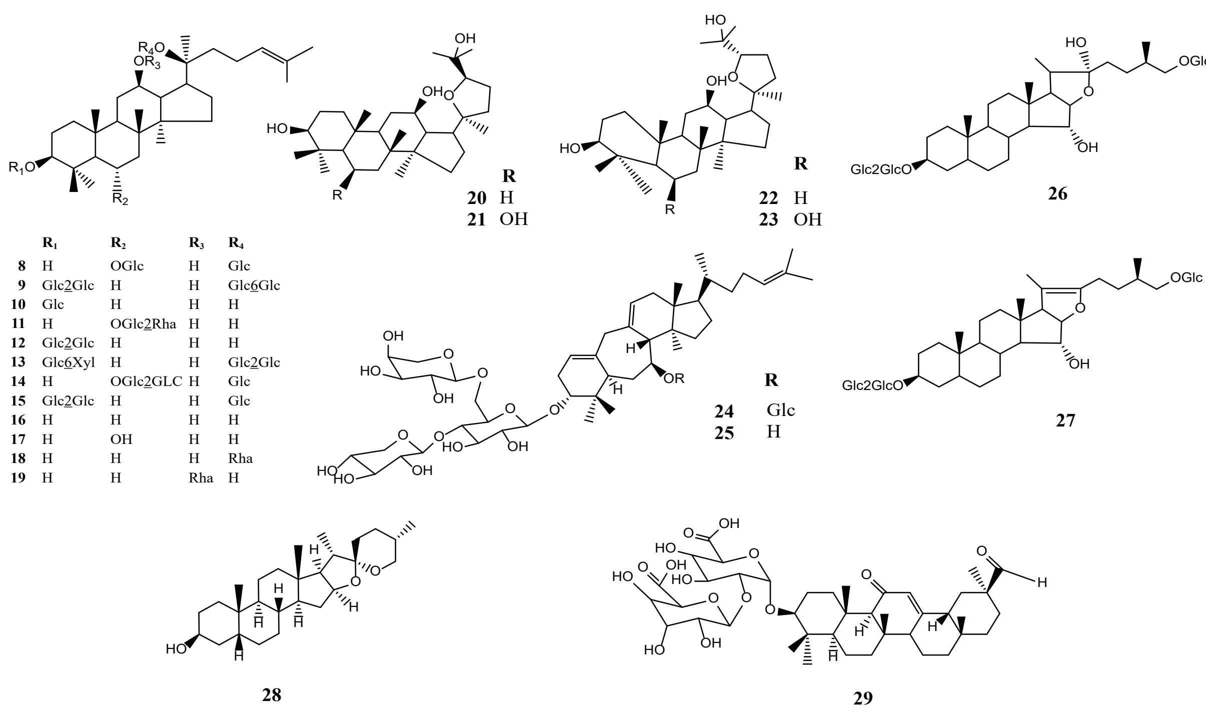

Figure 5 The structures of saponins **8-29**

(**8**) Ginsenoside Rg1; (**9**) Ginsenoside Rb1; (**10**) Ginsenoside Rh2; (**11**) Ginsenoside Rg2; (**12**) Ginsenoside Rg3; (**13**) Ginsenoside Rb3; (**14**) Ginsenoside Re; (**15**) Ginsenoside Rd; (**16**) 20(*S*)-Protopanaxdiol; (**17**) 20(*S*)-Protopanaxatriol; (**18**) Dammara-3-*O*-*α*-L-rhamnosy-l3*β*,12*β*,20-triol; (**19**) Dammara-12-*O*-*α*-L-rhamnosy-l3*β*,12*β*,20-triol; (**20**) Dammara-20(*S*),24(*R*)-epoxy3*β*,12*β*,25-triol; (**21**) Dammara-20(*S*),24(R)-epoxy3*β*,6*β*,12*β*,25-tetrol; (**22**) Dammara-20(*S*),24(*S*)-epoxy-3*β*,12*β*,25-triol; (**23**) Dammara 20(*S*),24(*S*)-epoxy3, 6*β*,12*β*,25*β*-tetrol; (**24**) Cyprotusides A; (**25**) Cyprotusides B; (**26**) Timosaponin B-II; (**27**) Timosaponin B-III; (**28**) Sarsasapogenin; (**29**) Glycyrrhizic acid.

Table 2 Total flavonoids extracts with antidepressant activity

Source	Antidepressant activity/Machanism	Reference
Yinyanghuo (Epimedium Brevicornum)	Improving the level of monoamine neurotransmitters such as NA, 5-HT in different regions of the brain	[56]
Gancao (Glycyrrhizae Radix et Rhizoma)	Reducing the elevation of serum corticosterone induced by chronic stress, enhancing brain 5-HT nerve function, and regulating the expression of key synaptic plasticity proteins	[80-82]
Suanzaoren (Semen Ziziphi Spinosae)	Shortening the immobility time of depressed mice in FST and TST	[83]
Xuancao (Hemerocallis Fulva)	Increasing of 5-HT, NE, and DA levels in the brain, and inhibiting excessive hyperstimulation of HPA axis	[84]
Yuxingcao (Houttuyniae Herba)	Alleviating corticosterone-induced cell damage	[85]
Shiliu (Punica granatum L.)	Improving chronic unpredictable mild stress (CUMS)-induced depressive symptoms	[86]
Zanghonghua (Crocus sativus L.)	Shortening the immobility time of depressed mice in FST and TST	[87]
Huluba (*Trigonella foenum-graecum L.*)	Exhibiting antidepressant-like effect by down-regulating KLF11/SIRT1-MAO-A pathway, up-regulating monoamine neurotransmitter levels, and inhibiting MAO-A expression	[88]

production and NOD-like receptor protein 3 (NLRP3) inflammasome activation in the rat brain [90, 91]. Chuanchenin (**31**), which was detected from Chenpi (Citri Reticulatae Pericarpium), also has remarkable antidepressant effect via regulating 5-HT_{1A}, 5-HT_2, α_1-epinephrine, DA-D1, and DA-D2 receptors [92]. Luteolin (**32**), a natural flavonoid existing in many plant-derived foods or medicines, exerts antidepressant effect on depressed mice by inhibiting the expression of endoplasmic reticulum stress-related proteins [93]. In addition, Daji (Cirsii Japonici Herba) displayed significant antidepressant effect mainly due to the presence of Luteolin, possibly by enhancement of γ-aminobutyric acid A (GABAA) receptor Cl-ion channel complex [94]. Naringin (**33**), which was isolated from Youzi (*Citrus maxima*), has antidepressant activity by increasing the concentrations of 5-HT, NE, and GR, as well as reducing the content of CORT and modulating the expression of BDNF/Nrf2 in the hippocampus of the depressed mice [95, 96]. Naringin (**34**), hesperidin (**35**), and neohesperidin (**36**) detected in Ganju (Citri Reticulatae Pericarpium Blanco) possess remarkable antidepressant effect with inhibition of MAO-A activity [50]. Compound **35** elicits antidepressant effect in mice possibly via the enhancement of Glo-1 function, the activation of the nuclear erythroid 2-related factor 2/antioxidant response element (Nrf2/ARE) signaling pathway, inhibition of L-arginine-nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) pathway [97-99].

3.4.3 Flavonol and its glycosides Quercetin (**37**), a flavonol compound isolated from Honggua (Carthami Flos), showed antidepressant effect and significantly shortened the immobility time in FST of depressed mice [100]. Kaempferol (**38**) and quercitirin (**39**), widely distributed in plant-derived medicines and foods, were isolated from Xianrenzhangguo (*Opuntia ficus-indica*) and displayed significant antidepressant activity by decreasing the immobility time in FST and TST of depressed mice [101]. The antidepressant mechanism of hyperoside (**40**) in Luobuma (*Apocynum venetum*) has been related to the regulation of the 5-HT_{2a} receptor [102]. Icariin (**41**), a flavanol glycoside isolated from Yinyanghuo (Epimedii Folium), exhibits its considerable antidepressant effect by reduction of corticotropin-releasing factor (CRF), monoamine neurotransmitters, and monoamine oxidase activity, altering the expression of glucocorticoid receptor and promotion of hippocampus neurogenesis [103-107].

3.4.4 Isoflavone and chalcones The antidepressant mechanism of isoflavones in Gegen (Puerariae Lobatae Radix) may be linked to monoaminergic neurons in the nervous system [108]. For example, Puerarin (**42**), one of the vital isoflavone compounds identified from it, displayed significant antidepressant activity by up-regulating the contents of monoamine neurotransmitters such as 5-HT, NE, and DA in brain tissue, and inhibiting the damage and apoptosis of hippocampal neurons in depressed mice [109]. It can also reduce CUMS-induced depression-like behavior in rats by reducing pro-inflammatory factors, increasing anti-inflammatory factors, remodeling their gut microbiota, and modulating hippocampal glucagon-like peptide 1 receptor/brain-derived neurotrophic factor/TrkBtyrosine kinase receptor B (GLP-1R/BDNF/TrkB) signaling to alleviate CUMS-induced depression-like behavior in rats [110-112]. Two chalcone compounds, isoliquiritin (**43**) and liquiritin (**44**), isolated from Gancao (Glycyrrhizae Radix et Rhizoma), could shorten the FST and TST in depressed mice, and their mechanism of antidepressant effect may be linked to the elevation of 5-HT and NE levels in the hippocampus, hypothalamus, and cortex [113]. Additionally, compound **44** may attenuate depression-like behavior via antioxidant stress and inhibition of NLRP3 inflammasome activation in the hippocampus [114]. The structures of flavonoids **30-44** with significant antidepressant activity are shown in Figure 6.

3.5 Phenylpropanoids

3.5.1 Phenylpropanoic acids Dehydrogingerone (**45**), a common phenylpropanoid isolated from Shengjiang (Zingiberis Rhizoma Recens), showed antidepressant activity related to 5-HT and NE [115]. Danshensu (**46**) and salvianolic acid B (**47**), identified from Danshen (Salviae Miltiorrhizae Radix et Rhizoma), possessed significant antidepressant activity. The antidepressant mechanism of the former is related to inhibiting the hyperactivity of the HPA axis, increasing the release of monoamine neurotransmitters in the hippocampus and activating CREB/BDNF pathway [116]. The latter relieves CMS-induced depressive-like state by activation of NLRP3 inflammasome and the adenylate-activated protein kinase/silent information regulator 1 (AMPK/SIRT1) signaling pathway [117, 118].

3.5.2 Coumarins Psoralen (**48**) and psoralidin (**49**) are common coumarin-type compounds identified from Buguzhi (Psoraleae Fructus). The former could reverse the increase in CRF and CORT concentrations caused by FST stress via elevation of 5-HT and 5-HIAA levels, thereby ameliorating the HPA axis function to play an antidepressant role [119], while the antidepressant mechanism of the latter may have a relation to increasing the contents of 5-HT, 5-HIAA, and DA, and decreasing the contents of adreno-cortico-tropic-hormone (ACTH), CRF, and corticosterone in serum [120]. In addition, scopolamine (**50**) isolated from Yuanzhi (Polygalae Radix) exhibits antidepressant effect via increasing the levels of 5-HT, NA, and DA [121], and auraptenol (**51**) reported from Baizhi (Angelicae Dahuricae Radix) exerts the same activity by regulating the 5-HT_{1A} receptor [122].

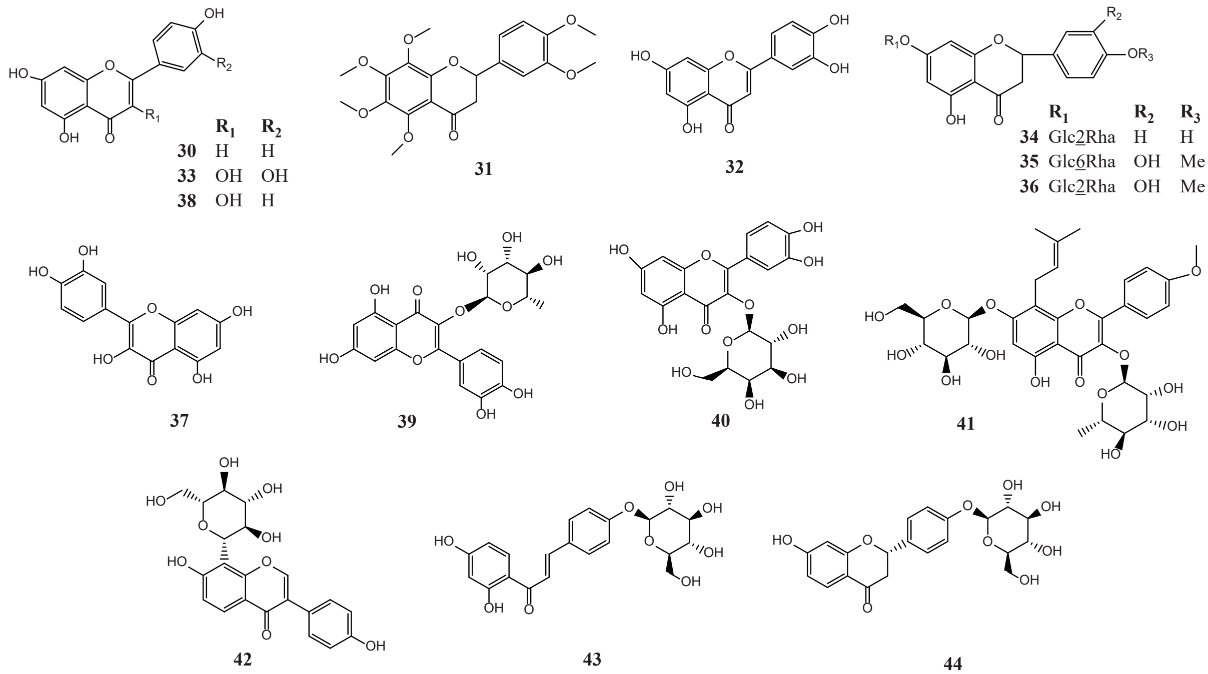

Figure 6 The structures of flavonoids **30-44**

(**30**) Apigenin; (**31**) Nobiletin; (**32**) Luteolin; (**33**) Naringenin; (**34**) Naringin; (**35**) Hesperidin; (**36**) Neohesperidin; (**37**) Quercetin; (**38**) Kaempferol; (**39**) Quercitirin; (**40**) Hyperoside; (**41**) Icariin; (**42**) Puerarin; (**43**) Isoliquiritin; (**44**) Liquiritin

3.5.3 Lignans Magnolol (**52**) and honokiol (**53**), two lignan compounds isolated from Houpo (Magnoliae Officinalis Cortex), are suggested to be helpful in the treatment of depression. The mechanism of compound **52** is associated with the elevation of BDNF expression in mice's hippocampus and frontal cortex, the accentuation of 5-HT system function, the enhancement of hippocampal neurogenesis, and neurotrophin-related intracellular signaling as well as the modulation of the HPA axis [123, 124]. A study has demonstrated that it can reduce the increase of proinflammatory cytokines IL-1β, IL-6, and tumor necrosis factor-α (TNF-α) in the prefrontal cortex of mice exposed to chronic mild stress [125]. Furthermore, the mixture of the two compounds could reverse the decrease of 5-HT in the brain regions of the depressed mice and increase the levels of 5-HT and 5-HIAA [126]. Rosmarinic acid (**54**) in Zisu (*Perilla frutescens*) can up-regulate BDNF levels in the hippocampus and hippocampus-derived astrocytes and activate BDNF/Nrf2 signaling and autophagy pathway [127, 128]. Rosavin (**55**) was identified and isolated from Hongjingtian (Rhodiolae Crenulatae Radix et Rhizoma), and exhibited significant antidepressant effect by the suppression of NA and DA reuptake, thereby increasing the content of NA and DA in the synaptic cleft [50]. The structures of flavonoids **45**-**55** with significant antidepressant activity are shown in Figure 7.

3.6 Phenols

Four phenol-type compounds, maned curcumin (**56**), demethoxycurcumin (**57**), bisdemethoxycurcumin (**58**), and tetrahydrocurcumin (**59**) were observed from Jianghuang (Curcumae Longae Rhizoma) and displayed significant antidepressant effect. Among them, curcumin (**56**), a diarylheptane compound, showed antidepressant effect in different animal models of depression by repressing monoamine oxidase and enhancing the levels of 5-HT and DA, reducing levels of inflammatory cytokines such as IL-1β and TNF-α, activating the mitogen-activated protein kinase/extracellar-signal-regulation kinase (MAPK/ERK) and Nrf2-ARE signaling pathways, as well as regulating hippocampal neuronal midbrain-derived neurotrophic factor [129-137]. α-Tocopherol (**60**) from Yumi (Zea Mays) was reported to possess antidepressant effect via significantly reducing the immobility time of TST induced by TNF-α in the depressed mice [138]. Gastrodin (**61**) displayed antidepressant effect by attenuating the levels of inflammatory factors TNF-α, IL-6, IL-17, and IL-1β in the hippocampus, protecting hippocampal neural stem cells (NSCs) against the proinflammatory cytokine IL-1β, and elevating the content of BDNF [139-141]. The antidepressant effect of methyl jasmonate (**62**) reported from Gancao (Glycyrrhizae Radix et Rhizoma) is related with the modulation of 5-HT and NE [21]. The structures of phenolic compounds **56**-**62** with significant antidepressant activity are shown in Figure 8.

3.7 Carbohydrates

Chrysanthemum oligosaccharides (**63**), the primary active ingredient of Xuelianguo (*Smallanthus sonchifolius*), shows the same antidepressant activity as the positive

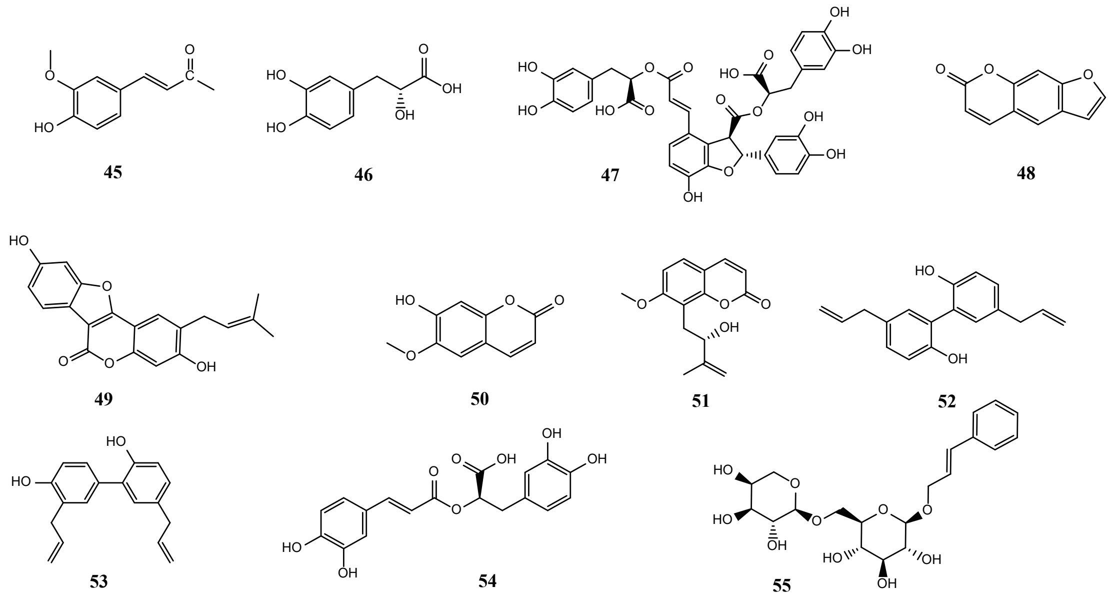

Figure 7 The structures of penylpropanoids **45**-**55**

(**45**) Dehydrozingerone; (**46**) Tanshinone; (**47**) Salvianolic acids; (**48**) Psoralen; (**49**) Psoralidin; (**50**) Scopoletin; (**51**) Auraptenol; (**52**) Magnolol; (**53**) Honokiol; (**54**) Rosmarinic acid; (**55**) Rosavin.

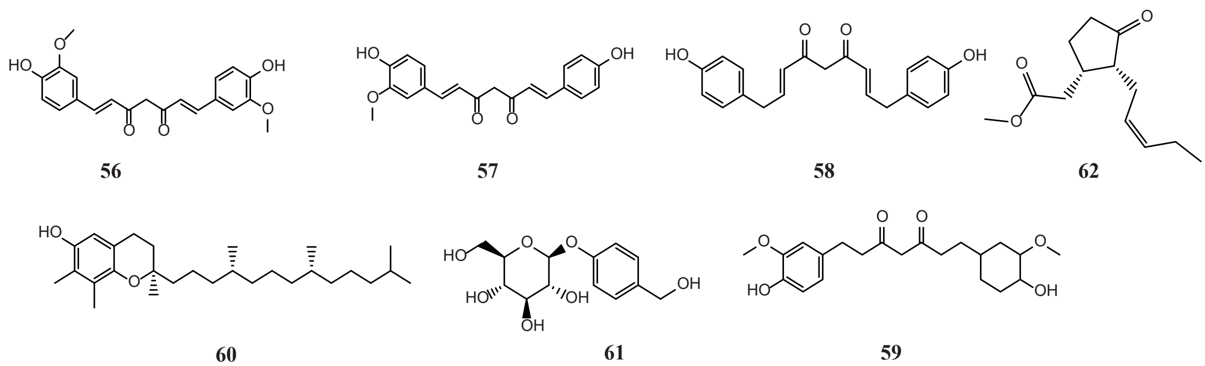

Figure 8 The structures of phenolics **56**-**62**

(**56**) Curcumin; (**57**) Demethoxycurcumin; (**58**) Dimethoxycurcumin; (**59**) Tetrahydrocurcumin; (**60**) α-Tocopherol; (**61**) Gastrodin; (**62**) Methyl jasmonate.

drug desipramine [142]. The structure of chrysanthemum oligosaccharides (**63**) is similar to that of chrysanthemum starch oligosaccharides reported from Bajitian (Morindae Officinalis Radix), which can antagonize depression-like behavior induced by chronic stress by regulating neurotrophic factor pathway and synaptic plasticity [143]. Nystose (**64**), 1F-Fructofuranosylnystose (**65**), chrysanthemum starch hexasaccharide (**66**), and chrysanthemum starch heptasaccharide (**67**) are four chrysanthemum starch oligosaccharides isolated from Bajitian (Morindae Officinalis Radix) with significant antidepressant activity [144]. 3,6'-Di mustard acyl sucrose (**68**) identified from Yuanzhi (Polygalae Radix) may generate antidepressant effect on drug-induced depression model mice via modulation of 5-HT and NE [145]. In addition, the polysaccharides extracted from Shaji (Hippohgae Fructus) and Xianggu (*Lentinula edodes*) displayed significant antidepressant effect by modulation of neurotransmitter levels [146, 147]. The structures of carbohydrates **63**-**68** with significant antidepressant activity are shown in Figure 9.

3.8 Alkaloids

Yongchongcao (*Cordyceps militaris*), a famous medicine and food homologous plant, has been listed as a new resource of food. Cordycepin (**69**) is its primary active component which can up-regulate the level of BDNF in the hippocampus of CUMS mice and down-regulate the level of the 5-HT2α receptor [148]. Piperine (**70**), a kind of cinnamphthalamide alkaloid abundant in Hujiao (Piperis Fructus), has remarkable antidepressant activity by regulating the proliferation, migration, and differentiation of neural stem cells as well as protecting and promoting functional nerve regeneration [149]; other researchers proposed that its mechanism is perhaps related to the upregulating of hippocampal BDNF levels and modulating

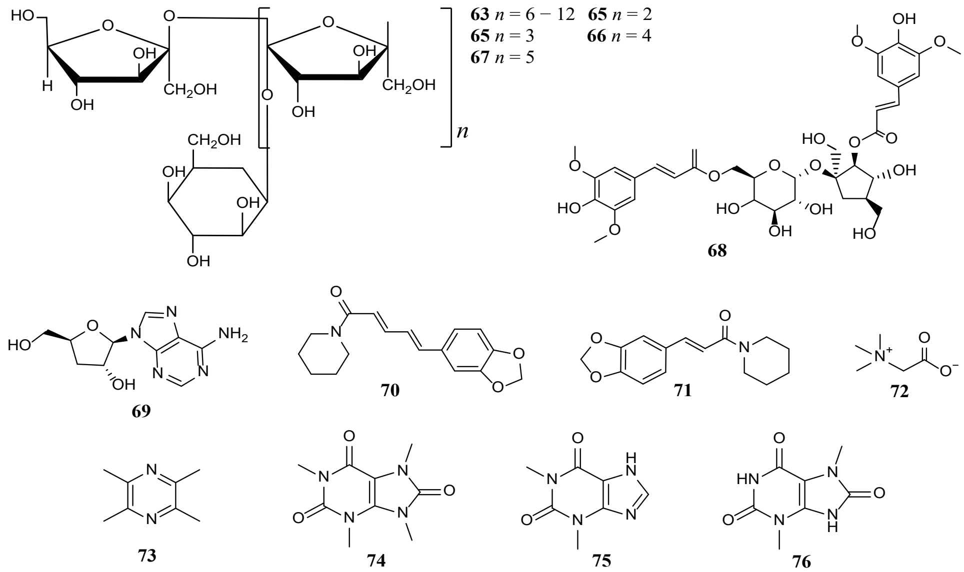

Figure 9 The structures of saccharides (**63**-**68**) and alkaloids (**69**-**76**)

(**63**) Chrysanthemum starch oligosaccharides; (**64**) Nystose; (**65**) 1F-Fructofuranosylnystose; (**66**) Chrysanthemum starch hexasaccharide I; (**67**) Chrysanthemum starch heptasaccharide II; (**68**) 3,6'-Di mustard acyl sucrose; (**69**) Cordycepin; (**70**) Piperine; (**71**) Antiepilepsirine; (**72**) Betaine; (**73**) Tetramethylpyrazine; (**74**) 1,3,7,9-Tetramethyluric acid; (**75**) Theophylline; (**76**) Theobromine.

the function of HPA axis [150, 151]. Anitiepilepsirinum (**71**), a derivative of piperine, regulated DA and 5-HT functions and attenuated MAO-A and B activity [152]. Betaine (**72**), which was the dominant bioactive compound of Digupi (Lycii Cortex), could dramatically regulate the function of 5-HT and NE [153]. Tetramethylpyrazine (**73**), a primary component with neuroprotective effect in Chuanxiong (Chuanxiong Rhizoma), probably displayed significant antidepressant effect by promoting BDNF signaling pathway and inhibiting toll like TLR4-NLRP3 inflammasome signaling pathway [154, 155]. In addition, three purine alkaloids named 1,3,7,9-tetramethyluric acid (**74**), theophylline (**75**), and cocoa alkaloids (**76**) identified from Chaye (*Camellia sinensis*) displayed significant antidepressant activity by ameliorating the disorder and metabolic abnormalities of monoamine neurotransmitters in the brain of the depressed mice. Among them, compound **74** has the most vigorous activity by modulating the neurological function of 5-HT and DA [156]. The structures of alkaloids **69**-**76** with significant antidepressant activity are shown in Figure 9.

3.9 Other types of compounds

Theanine (**77**), an amino acid identified in Chaye (*Camellia sinensis*), exerts antidepressant activity by regulating the central monoamine neurotransmitter system, reducing ACTH, CORT content, and cytokine expression, as well as inhibiting microglia activation [157, 158]. Three different intake methods (gavage, smelling, and feeding) of Tiancheng (*Citrus sinensis* Osbeck) essential oil can reverse the depressive behavior of the depressed mice and promote the release of monoamine neurotransmitters in the brain of mice; (+)-limonene (**78**), α-pinene (**79**), β-mene (**80**), and linalool (**81**) are the main volatile substances of the essential oil, which indicates that those volatile compounds may be the potential antidepressant ingredients [159]. Cycloastragalin (**82**) identified from Huangqi (Astragali Radix) could reduce the immobility time in FST of depressed mice by regulating the telomerase activity in the nerve cells [160]. 10-Hydroxydecenoic acid (**83**), a unique fatty acid in Fengwangjiang (Lac Regis Apis), effectively ameliorated depressive symptoms [161]. Cinnamaldehyde (**84**) displays significant depressive activity in middle-aged depressed rats by attenuating the expression and activity of cyclooxygenase-2 (COX-2) [162]. β-Amyrin palmitate (**85**), succinic acid (**86**), and β-carotene (**87**) are proved to be antidepressant monomers from Peilan (Eupatorii Herba) [163], Bajitian (Morindae Officinalis Radix) [144], and Huluobo (Daucus Carota) [164], respectively. The structures of compounds **77**-**87** with significant antidepressant activity are shown in Figure 10. In addition, the top six ingredients with antidepressant activity identified from medicine and food homologous products reported in the literature are shown in Figure 11, and all the compounds with significant antidepressant activity in this article are summarized in Table 3.

4 Discussion

Many complex substances are present in the crude extracts of plants, and different kinds of plants have different active ingredients. For example, in the ethanol extract of Hongjingtian (Rhodiolae Crenulatae Radix et Rhizoma), which includes phenylpropanoids and

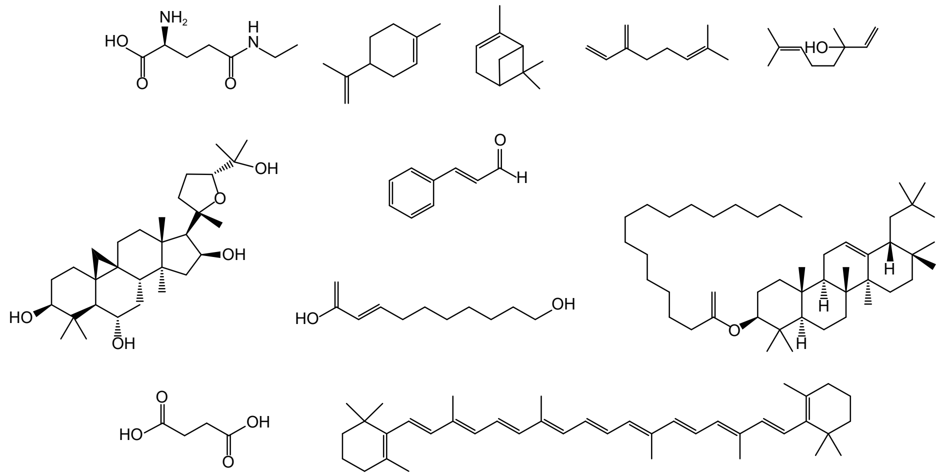

Figure 10 The structures of compounds **77-87**

(**77**) L-theanine; (**78**) (+)-Limonene; (**79**) α-Pinene; (**80**) β-Mene; (**81**) Linalool; (**82**) Cycloastragenol; (**83**) 10-Hydroxydecenoic acid; (**84**) Cinnamic aldehyde; (**85**) β-Amyrin palmitate; (**86**) Succinic acid; (**87**) β-Carotene.

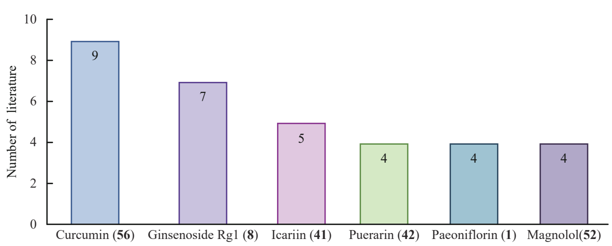

Figure 11 The top six ingredients identified from medicine and food homologous products with antidepressant activity reported in the literature

flavonoids, more than 10 compounds have been identified with significant inhibition activity for MAO-A [27]. However, none of the identified substances can achieve the same effect as the crude extraction. Therefore, it is speculated that the high activity may come from the synergistic effects of all the components in the extract. Several studies have only proved the antidepressant activity of the extract, leaving its specific components, which deserve further investigation, aside [35, 38]. A large number of studies have shown that active ingredients contained in foods have specific antidepressant effects [89, 95]; however, these studies are mainly based on preclinical trials, using a variety of experimental analyses and animal models of depression, and their structure-activity relationship, dose-effect relationship, and molecular mechanism still need further study. More importantly, the lack of in-depth study of antidepressant mechanisms has, in turn, limited the development of these functional foods. The poor industrialization of advanced processing technologies such as extraction, purification, refining and structural modification restricts products' prospect and added value [165].

The traditional treatment means (synthetic drugs) for depression has serious side effects, including sexual dysfunction, nausea, and gastrointestinal discomfort, which will bring great pain to depression patients [13-15]. In comparison, mild food therapy may effectively compensate for the shortcomings of traditional treatment, and some of the plant-derived compounds, such as sarsasapogenin and puerarin, also boast multi-target antidepressant effect [78, 109]. At present, integrated traditional Chinese and western medicine treatment also has become a common treatment method, reducing toxicity and enhancing the antidepressant effect of drugs [166]. A recent study has reported that corticosterone plays a crucial role in the vicious cycle of obesity and depression [167]. In addition to promoting the expression of BDNF in the hippocampus of mice to exert antidepressant effect [96], naringenin can also increase hippocampal glucocorticoid receptors and reduce serum corticosterone levels [95]; naringenin exists in citrus fruits, which is rich in content and may be developed into a new type of weight loss, hypoglycemic, and antidepressant multi-purpose drug in the future.

5 Conclusion

Most of the reviews focus on the study of herbs or phytochemicals, but this paper summarizes the antidepressant activity of functional foods or medicine and food homologous products for the first time; on top of that, it is also the first to summarize the antidepressant activity of extracts or monomer compounds from functional foods or medicine and food homologous plants. A total of 32 extracts (including 8 flavonoid extracts), 87 active ingredients, and related mechanisms have been summarized from 67 plant-derived functional foods or medicine and food homologous products, which lays a foundation for developing novel anti-depressive drugs from these functional foods or medicine and food homologous products, and provides an alternative treatment option for depression.

Table 3 Compounds with significant antidepressant activity

Category	Source	No.	Compound	Reference
Terpenoids	Chishao (Paeonia Radix Rubra)	**1**	Paeoniflorin	[45-48]
		2	Albiflorin	[49]
	Xingbaogu (Pleurotus Eryngii)	**3**	Eryngiolide A	[50]
	Zhizi (Gardenia Fructus)	**4**	Genipin	[51]
	Jixuecao (Centella Herba)	**5**	Asiaticoside	[50, 52]
		6	Asiatic acid	[50]
		7	Madecassic acid	[50]
Saponins	Renshen (Gingseng Radix et Rhizoma)	**8**	Ginsenoside Rg1	[58-64]
		9	Ginsenoside Rb1	[65-67]
		10	Ginsenoside Rh2	[68]
		11	Ginsenoside Rg2	[69]
		12	Ginsenoside Rg3	[70]
		13	Ginsenoside Rb3	[71]
		14	Ginsenoside Re	[72]
		15	Ginsenoside Rd	[73]
		16	20(*S*)-Promiddleanaxdiol	[50]
		17	20(*S*)-Promiddleanaxatriol	[50]
		18	Dammara 3-*O*-α-L-rhamnosy-l3β,12β,20-triol	[74]
		19	Dammara-12-*O*-α-L-rhamnosy-l3β,12β,20-triol	[50]
		20	Dammara-20(*S*),24(*R*)-epoxy-3β,12β,25-triol	[50]
		21	Dammara-20(*S*),24(*R*)-epoxy3β,6β,12β,25-tetrol	[50]
		22	Dammara-20(*S*),24(*S*)-epoxy-3β,12β,25-triol	[50]
		23	Dammara-20(*S*),24(*S*)-epoxy-3β,6β,12β,25β-tetrol	[50]
	Xiangfu (Cyperi Rhizoma)	**24**	Cyprotusides A	[75]
		25	Cyprotusides B	[75]
	Zhimu (Anemarrhenae Rhizoma)	**26**	Timosaponin B-II	[76]
		27	Timosaponin B-III	[77]
		28	Sarsasapogenin	[78]
	Gancao (Glycyrrhizae Radix et Rhizoma)	**29**	Glycyrrhizic acid	[79]
Flavonoids	Zisu (Perilla Frutescens)	**30**	Apigenin	[89]
	Ganju (Citri Reticulatae Pericarpium Blanco)	**30**	Apigenin	[90, 91]
	Chenpi (Citri Reticulatae Pericarpium)	**31**	Nobiletin	[92]
	Daji (Cirsii Japonici Herba)	**32**	Luteolin	[93, 94]
	Ganju (Citri Reticulatae Pericarpium Blanco)	**33**	Naringenin	[95, 96]
		34	Naringin	[50]
		35	Hesperidin	[97, 98]
		36	Neohesperidin	[50]
	Honggua (Carthami Flos)	**37**	Quercetin	[100]
	Xianrenzhangguo (Opuntia Ficus-Indica)	**38**	Kaempferol	[101]
		39	Quercitirin	[101]
	Luobuma (Apocynum Venetum)	**40**	Hyperoside	[102]
	Yinyanghuo (Epimedii Folium)	**41**	Icariin	[103-107]
	Gegen (Puerariae Lobatae Radix)	**42**	Puerarin	[109-112]
	Gancao (Glycyrrhizae Radix et Rhizoma)	**43**	Isoliquiritin	[113]
		44	Liquiritin	[113]

Table 3 Continued

Category	Source	No.	Compound	Reference
Phenyl-propanoids	Shengjiang (Zingiberis Rhizoma Recens)	**45**	Dehydrozingerone	[115]
	Danshen (Salviae Miltiorrhizae Radix et Rhizoma)	**46**	Tanshinone	[116]
		47	Salvianolic acids B	[117, 118]
	Buguzhi (Psoraleae fructus)	**48**	Psoralen	[119]
		49	Psoralidin	[120]
	Yuanzhi (Polygalae Radix)	**50**	Scopoletin	[121]
	Baizhi (Angelicae Dahuricae Radix)	**51**	Auraptenol	[122]
	Houpo (Magnoliae Officinalis Cortex)	**52**	Magnolol	[123-126]
		53	Honokiol	[126]
	Zisu (Perilla Frutescens)	**54**	Rosmarinic acid	[127, 128]
	Hongjingtian (Rhodiolae Crenulatae Radix et Rhizoma)	**55**	Rosavin	[50]
Phenols	Jianghuang (Curcumae Longae Rhizoma)	**56**	Curcumin	[129-137]
		57	Demethoxycurcumin	[50]
		58	Dimethoxycurcumin	[50]
		59	Tetrahydrocurcumin	[50]
	Yumi (Zea Mays)	**60**	α-Tocopherol	[138]
	Tianma (Gastrodiae Rhizoma)	**61**	Gastrodin	[139-141]
	Gancao (Glycyrrhizae Radix et Rhizoma)	**62**	Methyl jasmonate	[21]
Carbohydrates	Xuelianguo (Smallanthus Sonchifolius)	**63**	Chrysanthemum starch oligosaccharides	[142]
	Bajitian (Morindae Officinalis Radix)	**64**	Nystose	[144]
		65	1F-Fructofuranosylnystose	[144]
		66	Chrysanthemum starch hexasaccharide I	[144]
		67	Chrysanthemum starch heptasaccharide II	[144]
	Yuanzhi (Polygalae Radix)	**68**	3,6'-Di mustard acyl sucrose	[145]
Alkaloids	Yongchongcao (Cordyceps Militaris)	**69**	Cordycepin	[148]
	Hujiao (Piperis Fructus)	**70**	Piperine	[149-151]
		71	Antiepilepsirine	[152]
	Digupi (Lycii Cortex)	**72**	Betaine	[153]
	Chuanxiong (Chuanxiong Rhizoma)	**73**	Tetramethylpyrazine	[154, 155]
	Chaye (*Camellia sinensis*)	**74**	1,3,7,9-Tetramethyluric acid	[156]
		75	Theophylline	[156]
		76	Theobromine	[156]
Other types of compounds	Chaye (*Camellia sinensis*)	**77**	L-theanine	[157, 158]
	Tiancheng (*Citrus sinensis* Osbeck)	**78**	(+)-Limonene	[159]
		79	α-Pinene	[159]
		80	β-Mene	[159]
		81	Linalool	[159]
	Huangqi (Astragali Radix)	**82**	Cycloastragenol	[160]
	Fengwangjiang (Lac Regis Apis)	**83**	10-Hydroxydecenoic acid	[161]
	Rougui (Cinnamomi Cortex)	**84**	Cinnamic aldehyde	[162]
	Peilan (Eupatorii Herba)	**85**	β-Amyrin palmitate	[163]
	Bajitian (Morindae Officinalis Radix)	**86**	Succinic acid	[144]
	Huluobo (Daucus Carota)	**87**	β-Carotene	[164]

Fundings

National Key Rearch and Development Program of China (2021YFD1600301), Scientific Research Cooperation Project of Datong Daylily Industial Development Research Institute (2022QT003-3), Hunan Provincial Natural Science Foundation of China (2021JJ40245), Hong Kong Scholars Program (2021-164), and Hunan Provincial Key Research and Development Project (2020NK2031).

Competing interests

The authors declare no conflict of interest.

References

[1] GAUTUM S, JAIN A, GAUTAM M, et al. Clinical practice guidelines for the management of depression. Indian Journal of Psychiatry, 2017, 59(Supp11): S34–S50.
[2] FRIEDRICH MJ. Depression is the leading cause of disability around the world. JAMA, 2017, 317(15): 1517.
[3] HUANG YQ, WANG Y, WANG H, et al. Prevalence of mental disorders in China: a cross-sectional epidemiological study. The Lancet Psychiatry, 2019, 6(3): 211–224.
[4] WANG CY, PAN RY, WAN XY, et al. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. International Journal of Environmental Research and Public Health, 2020, 17(5): 1729.
[5] DRAGIOTI E, TSARTSALIS D, MENTIS M, et al. Impact of the COVID-19 pandemic on the mental health of hospital staff: an umbrella review of 44 meta-analyses. International Journal of Nursing Studies, 2022, 131: 104272.
[6] RACINE N, MCARTHUR BA, COOKE JE, et al. Global prevalence of depressive and anxiety symptoms in children and adolescents during COVID-19: a meta-analysis. JAMA Pediatrics, 2021, 175(11): 1142–1150.
[7] COVID-19 Mental Disorders Collaborators. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. Lancet, 2021, 398(10312): 1700–1712.
[8] GUO X, MENG Z, HUANG G, et al. Meta-analysis of the prevalence of anxiety disorders in mainland China from 2000 to 2015. Scientific Reports, 2016, 6: 28033.
[9] GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the global burden of disease study 2019. The Lancet Psychiatry, 2022, 9(2): 137–150.
[10] KARROURI R, HAMMANI Z, BENJELLOUN R, et al. Major depressive disorder: validated treatments and future challenges. World Journal of Clinical Cases, 2021, 9(31): 9350–9367.
[11] LIANG CS, CHUNG CH, TSAI CK, et al. In-hospital mortality among electroconvulsive therapy recipients: a 17-year nationwide population-based retrospective study. European Psychiatry, 2017, 42: 29–35.
[12] CIPRIANI A. Review: selective serotonin reuptake inhibitors as effective as tricyclic antidepressants for major depression, and may have fewer adverse effects. Evidence-Based Mental Health, 2003, 6(4): 117.
[13] JIANG HY, CHEN HZ, HU XJ, et al. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal bleeding: a systematic review and meta-analysis. Clinical Gastroenterology and Hepatology, 2015, 13(1): 42–50.
[14] CLAYTON AH, CROFT HA, HANDIWALA L. Antidepressants and sexual dysfunction: mechanisms and clinical implications. Postgraduate Medicine, 2014, 126(2): 91–99.
[15] FAVA GA, GATTI A, BELAISE C, et al. Withdrawal symptoms after selective serotonin reuptake inhibitor discontinuation: a systematic review. Psychotherapy and Psychosomatics, 2015, 84(2): 72–81.
[16] SCOTT AB, ENID MH, JANELLE YL, et al. Discontinuing or switching selective serotonin-reuptake inhibitors. Annals of Pharmacotherapy, 2002, 36(4): 578–584.
[17] HANSEN RA, GARTIEHNER G, LOHR KN, et al. Efficacy and safety of second-generation antidepressants in the treatment of major depressive disorder. Annals of Internal Medicine, 2005, 143(6): 415–426.
[18] KENNEDY SH, ANDERSEN HF, THASE ME. Escitalopram in the treatment of major depressive disorder: a meta-analysis. Current Medical Research and Opinion, 2009, 25(1): 161–175.
[19] TRIVEDI MH, RUSH AJ, WISNIEWSKI SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. The American Journal of Psychiatry, 2006, 163(1): 28–40.
[20] MA R, LI S, WANG Z, et al. Screening of effective antidepressant part from *Coreopsis tinctoria* and study on its mechanism. China Pharmacy, 2022, 33(10): 1177–1182.
[21] ROODABEH B, MOHAMMAD HF, MARZIEH SF, et al. Phytochemical constituents as future antidepressants: a comprehensive review. Nature Reviews Neuroscience, 2015, 26(6): 699–719.
[22] XU P, ZHANG CP, ZHOU T. Research progress of traditional Chinese medicine in improving pathogenesis of depression. China Journal of Experimental Traditional Medical Formulae, 2021, 27(9): 244–250.
[23] ZHOU BH, LI XJ, FENG Qi, et al. Antidepressant activity of ethanolic extracts of *Gastrodia elata* in mice. Chinese Journal of Hospital Pharmacy, 2007, (11): 1525–1528.
[24] KANG M, SHIN D, OH JW, et al. The anti-depressant effect of Nelumbinis Semen on rats under chronic mild stress induced depression-like symptoms. The American Journal of Chinese Medicine, 2005, 33(2): 205–213.
[25] YAN B, WANG DY, XING DM, et al. The antidepressant effect of ethanol extract of Radix Puerariae in mice exposed to cerebral ischemia reperfusion. Pharmacology, Biochemistry and Behavior, 2004, 78(2): 319–325.
[26] WANG JM, WANG S, CUI Y. Antidepressant activities of extracts from *Gynostemma Pentaphyllum* (Thunb) Makino. Lishizhen Medicine and Metaria Medica Research, 2012, 23(4): 815–817.
[27] VAN DD, MARSTON A, BRAVO J, et al. Monoamine oxidase inhibition by *Rhodiola rosea* L. roots. Journal of Ethnopharmacology, 2009, 122(2): 397–401.
[28] WANG CZ. Studies on chemcial constituents and antidepressant effect of different parts from *Platycodon granfiflorum*. Changchun: Jilin University, 2018.
[29] VERONIKA B, SANSEI N, TSUTOMU S, et al. Antidepressant

effects of *Apocynum venetum* leaves in a forced swimming test. Biological and Pharmaceutical Bulletin, 2001, 24(7): 848–851.

[30] ZHAN J. Study on the anti-depressant and anti-fatigue active ingredients of Morindae Officinalis Radix How. Wuxi: Southern Yangtze University, 2019.

[31] LIU ZG, LIU XN, LUO SY, et al. Extract of sesame cake and sesamol alleviate chronic unpredictable mild stress-induced depressive-like behaviors and memory deficits. The Journal of Functional Foods, 2018, 42: 237–247.

[32] NITA P; RACHMAT H; ZISKE M, et al. Antidepressant effect of Cinnamon (*Cinnamomum burmannii*) Bark extract in chronic stress-induced rats. Open Access Macedonian Journal of Medical Sciences, 2020, 8(A): 273–277.

[33] HWANG KA, HWANG HJ, HWANG YJ, et al. Mustard leaf extract suppresses psychological stress in chronic restraint stress-subjected mice by regulation of stress hormone, neurotransmitters, and apoptosis. Nutrients, 2020, 12(12): 3640.

[34] YU ZF, KONG LD, CHEN Y. Antidepressant activity of aqueous extracts of Curcumae Longae Rhizoma in mice. Journal of Ethnopharmacology, 2002, 83(1-2): 161–165.

[35] WANG JM, XIN R. Antidepression activity of extract of Heshouwu (Radix Polygoni Multiflori). Journal of Beijing University of Traditional Chinese Medicine, 2012, 35(7): 449–451, 455.

[36] LIU MH, WANG SR, LIU P, et al. Repairing effect of Fructus Schisandrae Chinensis extracts on hippocampal neuron injury in depressed rats and its mechanism. Hunan Journal of Traditional Chinese Medicine, 2022, 39(5): 1129–1135.

[37] HE DY. Studies on antidepressant-like effects of aqueous of *Camellia euphlebia* Leaves. Dalian: Dalian University of Technology, 2018.

[38] LI MQ. Studies on anti-depressant activity of Okra seed and related mechanism in mice. Tianjin: Tianjin University of Science and Technology, 2016.

[39] IROGHAMA IA, OSARETIN ATE, MARIAM NIE. Role of monoaminergic neurotransmission on the antidepressant effect of leaf and root extracts of *Rauwolfia vomitoria* on the locomotion and immobility of Sprague-Dawley rats. European Journal of Medicinal Plants, 2020: 45–55.

[40] KIM HR, LEE YJ, KIM TW, et al. *Asparagus cochinchinensis* extract ameliorates menopausal depression in ovariectomized rats under chronic unpredictable mild stress. BMC Complementary Medicine and Therapies, 2020, 20(1): 325–339.

[41] LV GY, CHEN SH, SU J, et al. Effects of different fractions from Cortex Eucommiae on oxidation resistance and anti-despondent of extradiol-induced kidney-Yang deficiency mice. Journal of Zhejiang Chinese Medical University, 2009, 33(5): 729–731.

[42] AI Z. Study on the antidepressant and sleep-improving effect and mechanism of Maca (*Lepidium meyenii*) extract. Wuhan: Huazhong University of Science and Technology, 2013.

[43] HAO CW, LAI WS, HO CT, et al. Antidepressant-like effect of lemon essential oil is through a modulation in the levels of norepinephrine, dopamine, and serotonin in mice: use of the tail suspension test. The Journal of Functional Foods, 2013, 5(1): 370–379.

[44] MESSAOUDI M, BISSON JF, NEJDI A, et al. Antidepressant-like effects of a cocoa polyphenolic extract in Wistar-Unilever rats. Nutritional Neuroscience, 2008, 11(6): 269–276.

[45] WANG XL, WANG YT, GUO ZY, et al. Efficacy of paeoniflorin on models of depression: a systematic review and meta-analysis of rodent studies. Journal of Ethnopharmacology, 2022, 290: 115067.

[46] XUE M, MU DZ, HUANG X. Effect of paeoniflorin on hippocamp tissue pathomorphology and BDNF level of forced swimming rats model. Journal of Nanjing University of Traditional Chinese Medicine, 2016, 32(5): 439–441.

[47] TANG M, CHEN M, LI Q. Paeoniflorin ameliorates chronic stress-induced depression-like behavior in mice model by affecting ERK1/2 pathway. Bioengineered, 2021, 12(2): 11329–11341.

[48] WANG X, FENG S, WANG Y, et al. Paeoniflorin: a neuroprotective monoterpenoid glycoside with promising anti-depressive properties. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology, 2021, 90: 153669.

[49] FU SN. Explore the mechanism of anti-depression of Albiflorin by regulating intestinal flora based on targeted metabolomics research methods. Tianjin: Tianjin University of Traditional Chinese Medicine, 2020.

[50] SUN CL, GENG CN, YIN XJ, et al. Natural products as antidepressants documented in Chinese patents from 1992 to 2013. Journal of Asian Natural Products Research, 2015, 17(2): 188–198.

[51] TIAN JS, CUI YL, HU LM, et al. Antidepressant-like effect of genipin in mice. Neuroscience Letters, 2010, 479(3): 236–239.

[52] LUO L, LIU XL, MU RH, et al. Hippocampal BDNF signaling restored with chronic asiaticoside treatment in depression-like mice. Brain Research Bulletin, 2015, 114: 62–69.

[53] FU CY, LIU YH, LI MJ, et al. Extraction and purification techniques and antidepression activity of total saponins from bulbs of *Lilium brownii*. Natural Product Research, 2012, (5): 118–122.

[54] XIANG H, LIU YX, ZHANG BB, et al. The antidepressant effects and mechanism of action of total saponins from the caudexes and leaves of *Panax notoginseng* in animal models of depression. Phytomedicine, 2011, 18(8): 731–738.

[55] ZHANG HL, ZHOU ZL, YANG HY, et al. Effects of total saponins in *Panax notoginseng* leaves on behavior and levels of cAMP, PKA, and BDNF in rats exposed to chronic unpredictable mild stress. Modern Food Science & Technology, 2015, (3): 19–23, 41.

[56] WU F. The effect of TSP/ TFE on experimental depreession, 5-HT in brain and β-adrenergic receptor. Modern Preventive Medicine, 2005, (7): 744–746, 764.

[57] ZHANG W, YU ZY, MEI TZ, et al. Antidepressant effect and mechanism of gross saponins of *Tribulus terrestris*. Chinese Pharmacological Bulletin, 2017, 33(3): 343–348.

[58] WANG J, SHEN FM, ZHANG ZR, et al. Effects of ginsenoside Rg1 on depression-like behaviors, expression of hippocampal synaptic proteins and activation of glial cells in stressed mice. Journal of Biology, 2021, 38(3): 26–30.

[59] HUANG Q, CHU SF, ZHANG JT, et al. Effects of ginsenoside Rg1 on anti-depression and synapic ultrastructure. Chinese Pharmacological Bulletin, 2013, 29(8): 1124–1127.

[60] ZHENG M, QIAN H, CHU SF, et al. Antidepressive effects of ginsenoside Rg1 via regulation of HPA and HPG axis. Biomedicine & Pharmacotherapy, 2017, 92: 962–971.

[61] LIU Z, QI Y, CHENG Z, et al. The effects of ginsenoside Rg1 on chronic stress induced depression-like behaviors, BDNF expression and the phosphorylation of PKA and CREB in rats.

Neuroscience, 2016, 322: 358–369.

[62] LOU YX, WANG ZZ, XIA CY, et al. The protective effect of ginsenoside Rg1 on depression may benefit from the gap junction function in hippocampal astrocytes. European Journal of Pharmacology, 2020, 882: 173309.

[63] WANG HQ, YANG YT, YANG SW, et al. Ginsenoside Rg1 ameliorates neuroinflammation via suppression of Connexin43 ubiquitination to attenuate depression. Frontiers in Pharmacology, 2021, 12: 709019.

[64] JIN C, WANG ZZ, ZHOU H, et al. Ginsenoside Rg1-induced antidepressant effects involve the protection of astrocyte gap junctions within the prefrontal cortex. Progress in Neuro-psychopharmacology & Biological Psychiatry, 2017, 75: 183–191.

[65] WANG GL, LEI C, TIAN Y, et al. Rb1, the primary active ingredient in *Panax ginseng* C. A. Meyer, exerts antidepressant-like effects via the BDNF-Trkb-CREB pathway. Frontiers in Pharmacology, 2019, 10: 1034.

[66] JIANG N, HUANG H, ZHANG Y, et al. Ginsenoside Rb1 produces antidepressant-like effects in a chronic social defeat stress model of depression through the BDNF–Trkb signaling pathway. Frontiers in Pharmacology, 2021, 12: 680903.

[67] GUO Y, XIE J, ZHANG L, et al. Ginsenoside Rb1 exerts antidepressant-like effects via suppression inflammation and activation of AKT pathway. Neuroscience Letters, 2021, 744: 135561.

[68] SHI L, JI C, LIU Y, et al. Ginsenoside Rh2 administration produces crucial antidepressant-like effects in a CUMS-induced mice model of depression. Brain and Behavior, 2022, 12(8): e2705.

[69] REN Y, WANG JL, ZHANG X, et al. Antidepressant-like effects of ginsenoside Rg2 in a chronic mild stress model of depression. Brain Research Bulletin, 2017, 134: 211–219.

[70] YOU Z, YAO Q, SHEN J, et al. Antidepressant-like effects of ginsenoside Rg3 in mice via activation of the hippocampal BDNF signaling cascade. Journal of Natural Medicines, 2017, 71(2): 367–379.

[71] CUI JH, JIANG LX, XIANG H. Ginsenoside Rb3 exerts antidepressant-like effects in several animal models. Journal of Psychopharmacology, 2012, 26(5): 697–713.

[72] LEE B, SHIM I, LEE H, et al. Effect of ginsenoside Re on depression- and anxiety-like behaviors and cognition memory deficit induced by repeated immobilization in rats. Journal of Microbiology and Biotechnology, 2012, 22(5): 708–720.

[73] LI Y, WANG ML, ZHANG B, et al. Antidepressant-like effect and mechanism of ginsenoside Rd on rodent models of depression. Drug Design Development and Therapy, 2022, 16: 843–861.

[74] JIANG N, WEI LJ, WANG H, et al. Ginsenoside 20(S)-protopanaxadiol attenuates depressive-like behaviour and neuroinflammation in chronic unpredictable mild stress-induced depressive rats. Behavioural Brain Research, 2020, 393: 112710.

[75] ZHOU ZL, LIN SQ, YIN WQ. New cycloartane glycosides from the rhizomes of *Cyperus rotundus* and their antidepressant activity. Journal of Asian Natural Products Research, 2016, 18(7): 662–668.

[76] LU MZ, ZHANG ZQ, YI J, et al. Study on the effect and mechanism of timosaponin B-Ⅱ on antidepressant. Journal of Pharmaceutical Practice, 2010, 28(4): 283–287.

[77] ZHANG XL, WANG L, XIONG L, et al. Timosaponin B-III exhibits antidepressive activity in a mouse model of postpartum depression by the regulation of inflammatory cytokines, BNDF signaling and synaptic plasticity. Experimental and Therapeutic Medicine, 2017, 14(4): 3856–3861.

[78] REN LX, LUO YF, LI X, et al. Antidepressant-like effects of sarsasapogenin from *Anemarrhena asphodeloides* BUNGE (Liliaceae). Biological & Pharmaceutical Bulletin, 2006, 29(11): 2304–2306.

[79] WANG B, LIAN YJ, DONG X, et al. Glycyrrhizic acid ameliorates the kynurenine pathway in association with its antidepressant effect. Behavioural Brain Research, 2018, 353: 250–257.

[80] GUO J, ZHAO WH, FAN ZZ, et al. Screening ingredients of traditional Chinese medicine with effect on inhibiting contraction of hepatic stellate cells induced by endothelin-1. Pharmacology and Clinics of Chinese Materia Medica, 2012, 28(6): 59–62.

[81] HUA B, CHENG RF, JING J, et al. Anti-depression effect of licorice flavonoids from *Glycyrrhiza uralensis* through promotion of central serotonergic neural function in mice. Chinese Journal of Pharmacology and Toxicology, 2014, 28(4): 484–490.

[82] HUA B, CHENG RF, JING J, et al. Antidepressant effect of licorice flavonoids from *Glycyrrhiza uralensis* on stress-induced depression and the key protein SYP/PSD95 associated with synaptic plasticity in rats. Chinese Journal of New Drugs, 2014, 23(10): 1180–1187.

[83] ZHAO QD, SHU LX, WANG Y, et al. Study on the antidepressant effect of total flavonoids from Semen Ziziphi Spinosae. Tianjin Journal of Traditional Chinese Medicine, 2011, 28(4): 335–337.

[84] DI JL. The investigation of anti-depression effect of *Hemerocallis fulva* flavonoids and related mechanism. Tianjin: Tianjin University of Science & Technology, 2016.

[85] GONG NC. The researches of extraction, purification and antidepressant effects of the extract of flavonoids of *Houttuynia cordata* Thunb. Wuhan: Hubei University of Technology, 2009.

[86] NAVEEN S, SIDDALINGASWAMY M, SINGSIT D, et al. Anti-depressive effect of polyphenols and omega-3 fatty acid from pomegranate peel and flax seed in mice exposed to chronic mild stress. Psychiatry and Clinical Neurosciences, 2013, 67(7): 501–508.

[87] WANG Y, HAN T, ZHU Y, et al. Antidepressant properties of bioactive fractions from the extract of *Crocus sativus* L.. Journal of Natural Medicines, 2010, 64(1): 24–30.

[88] WANG JC, CHENG CL, XIN C, et al. The Antidepressant-like effect of flavonoids from Trigonella Foenum-Graecum seeds in chronic restraint stress mice via modulation of monoamine regulatory pathways. Molecules, 2019, 24(6): 1105.

[89] NAKAZAWA T, YASUDA T, UEDA J, et al. Antidepressant-like effects of apigenin and 2,4,5-trimethoxycinnamic acid from *Perilla frutescens* in the forced swimming test. Biological and Pharmaceutical Bulletin, 2003, 26(4): 474–480.

[90] YI LT, LI JM, LI YC, et al. Antidepressant-like behavioral and neurochemical effects of the citrus-associated chemical apigenin. Life Sciences, 2008, 82(13): 741–751.

[91] LI RP, WANG XX, QIN TT, et al. Apigenin ameliorates chronic mild stress-induced depressive behavior by inhibiting interleukin-1beta production and NLRP3 inflammasome activation in the rat brain. Behavioural Brain Research, 2016,

296: 318–325.
[92] YI LT, XU HL, FENG J, et al. Involvement of monoaminergic systems in the antidepressant-like effect of nobiletin. Physiology & Behavior, 2011, 102(1): 1–6.
[93] ISHISAKA M, KAKEFUDA K, YAMAUCHI M, et al. Luteolin shows an antidepressant-like effect via suppressing endoplasmic reticulum stress. Biological & Pharmaceutical Bulletin, 2011, 34(9): 1481–1486.
[94] DE LA PEÑA JB, KIM CA , LEE HL, et al. Luteolin mediates the antidepressant-like effects of Cirsium Japonicum in mice, possibly through modulation of the GABAA receptor. Archives of Pharmacal Research, 2014, 37(2): 263–269.
[95] YI LT, LI J, LI HC, et al. Antidepressant-like behavioral, neurochemical and neuroendocrine effects of naringenin in the mouse repeated tail suspension test. Progress in Neuropsychopharmacol and Biological Psychiatry, 2012, 39(1): 175–181.
[96] YI LT, LIU BB, LI J, et al. BDNF signaling is necessary for the antidepressant-like effect of naringenin. Progress in Neuropsychopharmacoland Biological Psychiatry, 2014, 48: 135–141.
[97] XIE L, GU Z, LIU H, et al. The Anti-depressive effects of hesperidin and the reative mechanisms based on the NLRP3 inflammatory signaling pathway. Frontiers in Pharmacology, 2020, 11: 1251.
[98] ZHU X, LIU HY, LIU Y, et al. The Antidepressant-like effects of hesperidin in streptozotocin-induced diabetic rats by activating Nrf2/ARE/Glyoxalase 1 pathway. Frontiers in Pharmacology, 2020, 11: 1325.
[99] DE GOMES MG, DE GMG, GOES AT, et al. Hesperidin exerts antidepressant-like effects in acute and chronic treatments in mice: possible role of l-arginine-NO-cGMP pathway and BDNF levels. Brain Research Bulletin, 2014, 104: 19–26.
[100] RANDHAWA K, KUMAR D, JAMWAL A, et al. Screening of antidepressant activity and estimation of quercetin from Coccinia indica using TLC densitometry. Pharmaceutical Biology, 2015, 53(12): 1867–1874.
[101] PARK SH, SIM YB, HAN PL, et al. Antidepressant-like effect of kaempferol and quercitirin, isolated from *Opuntia ficus-indica* var. *saboten*. Experimental Neurobiology, 2010, 19(1): 30–38.
[102] ZHENG M, LIU C, PAN F, et al. Antidepressant-like effect of hyperoside isolated from *Apocynum venetum* leaves: possible cellular mechanisms. Phytomedicine, 2012, 19(2): 145–149.
[103] PAN Y, KONG L, XIA X, et al. Antidepressant-like effect of icariin and its possible mechanism in mice. Pharmacology Biochemistry and Behavior, 2005, 82(4): 686–694.
[104] XUE YL, XU JT, QIU JH, et al. Effect of icariin on depressive behavior and neuronal damage in depression rats. Journal of Clinical and Experimental Medicine, 2021, 20(20): 2152–2156.
[105] ZENG NX, LI HZ, WANG HZ, et al. Exploration of the mechanism by which icariin modulates hippocampal neurogenesis in a rat model of depression. Neural Regeneration Research, 2022, 17(3): 632–642.
[106] LIU B, XU C, WU X, et al. Icariin exerts an antidepressant effect in an unpredictable chronic mild stress model of depression in rats and is associated with the regulation of hippocampal neuroinflammation. Neuroscience, 2015, 294: 193–205.
[107] WU X, WU JF, XIA SJ, et al. Icaritin opposes the development of social aversion after defeat stress via increases of GR mRNA and BDNF mRNA in mice. Behavioural Brain Research, 2013, 256: 602–608.
[108] WANG HL, SHI TY. Experiment study on anti-depressant effects of pueraria isoflavone. Chinese Journal of Experimental Traditional Medical Formulae, 2012, 18(21): 268–271.
[109] WANG R, LIU JC, LUO CJ, et al. The neuroprtective effects of puerarin on mouse model of perimenopausal depression and possible mechanism. Chinese Journal of Neuroanatomy, 2017, 33(2): 190–196.
[110] SONG XJ, WANG WH, DING SS, et al. Exploring the potential antidepressant mechanisms of puerarin: anti-inflammatory response via the gut-brain axis. Journal of Affective Disorders, 2022, 310: 459–471.
[111] SONG XJ, WANG WH, DING SS, et al. Puerarin ameliorates depression-like behaviors of with chronic unpredictable mild stress mice by remodeling their gut microbiota. Journal of Affective Disorders, 2021, 290: 353–363.
[112] LIU Y, HU Z, WANG J, et al. Puerarin alleviates depressive-like behaviors in high-fat diet-induced diabetic mice via modulating hippocampal GLP-1R/BDNF/TrkB signaling. Nutritional Neuroscience, 2022: 1–14.
[113] WANG WX, HU XY, ZHAO ZY, et al. Antidepressant-like effects of liquiritin and isoliquiritin from *Glycyrrhiza uralensis* in the forced swimming test and tail suspension test in mice. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2007, 32(5): 1179–1184.
[114] LIU C, YUAN D, ZHANG C, et al. Liquiritin alleviates depression-like behavior in CUMS mice by inhibiting oxidative stress and NLRP3 inflammasome in hippocampus. Evidence-based Complementary and Alternative Medicine, 2022, 2022: 7558825.
[115] DÉBORA MM, ANGELITA B, ANGELA MC, et al. Antidepressant-like activity of dehydrozingerone: involvement of the serotonergic and noradrenergic systems. Pharmacology Biochemistry and Behavior, 2014, 127: 111–117.
[116] ZHONG SJ, ZHENG SC, QIU XY, et al. Anti-depressant effects of Danshensu sodium on chronic unpredicted mild stress mice. Chinese Journal of New Drugs, 2018, 27(23): 2819–2824.
[117] HUANG QT, YE X, WANG L, et al. Salvianolic acid B abolished chronic mild stress-induced depression through suppressing oxidative stress and neuro-inflammation via regulating NLRP3 inflammasome activation. Journal of Food Biochemistry, 2019, 43(3): e12742.
[118] LIAO DH, CHEN Y, GUO YJ, et al. Salvianolic acid B improves chronic mild stress-induced depressive behaviors in rats: involvement of AMPK/SIRT1 signaling pathway. Journal of Inflammation Research, 2020, 13: 195–206.
[119] XU Q, PAN Y, YI LT, et al. Antidepressant-Like effects of psoralen isolated from the seeds of Psoraleae Fructus in the mouse forced swimming test. Biological & Pharmaceutical Bulletin, 2008, 31(6): 1109–1114.
[120] YI LT, LI YC, PAN Y, et al. Antidepressant-like effects of psoralidin isolated from the seeds of Psoraleae Fructus in the forced swimming test in mice. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2007, 32(2): 510–519.

[121] CAPRA JC, CUNHA MP, MACHADO DG, et al. Antidepressant-like effect of scopoletin, a coumarin isolated from *Polygala sabulosa (Polygalaceae)* in mice: evidence for the involvement of monoaminergic systems. European Journal of Pharmacology, 2010, 643(2): 232–238.

[122] GU XS, ZHOU Y, WU XM, et al. Antidepressant-like effects of auraptenol in mice. Scientific Reports, 2014, 4(3): 4433.

[123] LI LF, LU J, LI XM, et al. Antidepressant-like effect of magnolol on BDNF up-regulation and serotonergic system activity in unpredictable chronic mild stress treated rats. Phytotherapy Research, 2012, 26(8): 1189–1194.

[124] BAI YT, SONG LH, DAI GL, et al. Antidepressant effects of magnolol in a mouse model of depression induced by chronic corticosterone injection. Steroids, 2018, 135: 73–78.

[125] CHENG J, DONG SQ, YI LT, et al. Magnolol abrogates chronic mild stress-induced depressive-like behaviors by inhibiting neuroinflammation and oxidative stress in the prefrontal cortex of mice. International Immunopharmacology, 2018, 59: 61–67.

[126] XU Q, YI LT, PAN Y, et al. Antidepressant-like effects of the mixture of honokiol and magnolol from the barks of Magnoliae Officinalis in stressed rodents. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2008, 32(3): 715–725.

[127] JIN X, LIU P, YANG FC, et al. Rosmarinic acid ameliorates depressive-like behaviors in a rat model of CUS and Up-regulates BDNF levels in the hippocampus and hippocampal-derived astrocytes. Neurochemical Research, 2013, 38(9): 1828–1837.

[128] YU Y, LI Y, QI KM, et al. Rosmarinic acid relieves LPS-induced sickness and depressive-like behaviors in mice by activating the BDNF/Nrf2 signaling and autophagy pathway. Behavioural Brain Research, 2022, 433: 114006.

[129] KULKARNI SK, BHUTANI MK, BISHNOI M. Antidepressant activity of curcumin: involvement of serotonin and dopamine system. Psychopharmacology, 2008, 201(3): 435–442.

[130] LIAO DH, LV CF, CAO LZ, et al. Curcumin attenuates chronic unpredictable mild stress-induced depressive-like behaviors via restoring changes in oxidative stress and the activation of Nrf2 signaling pathway in rats. Oxidative Medicine and Cellular Longevity, 2020, 2020: 9268083.

[131] WANG Y, WANG JM, MA H, et al. Research of the antidepressant of curcumin. The Chinese Journal of Clinical Pharmacology, 2022, 38(13): 1461–1465.

[132] ZHANG WY, GUO YJ, HAN WX, et al. Curcumin relieves depressive-like behaviors via inhibition of the NLRP3 inflammasome and kynurenine pathway in rats suffering from chronic unpredictable mild stress. International Immunopharmacology, 2019, 67: 138–144.

[133] FAN CQ, SONG QQ, WANG P, et al. Neuroprotective effects of curcumin on IL-1β-induced neuronal apoptosis and depression-like behaviors caused by chronic stress in rats. Frontiers in Cellular Neuroscience, 2018, 12: 516.

[134] YU JJ, PEI LB, ZHANG Y, et al. Chronic supplementation of curcumin enhances the efficacy of antidepressants in major depressive disorder: a randomized, double-blind, placebo-controlled pilot study. Journal of Clinical Psychopharmacology, 2015, 35(4): 406–410.

[135] LIU DX, WANG Z, GAO Z, et al. Effects of curcumin on learning and memory deficits, BDNF, and ERK protein expression in rats exposed to chronic unpredictable stress. Behavioural Brain Research, 2014, 271: 116–121.

[136] LAURA LH, LULI A, EVARISTUS N, et al. Antidepressant-like effects of curcumin in WKY rat model of depression is associated with an increase in hippocampal BDNF. Behavioural Brain Research, 2013, 239: 27–30.

[137] ZHANG L, XU TY, WANG S, et al. Curcumin produces antidepressant effects via activating MAPK/ERK-dependent brain-derived neurotrophic factor expression in the amygdala of mice. Behavioural Brain Research, 2012, 235(1): 67–72.

[138] MANOSSO LM, NEIS VB, MORETTI M, et al. Antidepressant-like effect of α-tocopherol in a mouse model of depressive-like behavior induced by TNF-α. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2013, 46: 48–57.

[139] WANG HN, ZHANG RG, QIAO YT, et al. Gastrodin ameliorates depression-like behaviors and up-regulates proliferation of hippocampal-derived neural stem cells in rats: involvement of its anti-inflammatory action. Behavioural Brain Research, 2014, 266: 153–160.

[140] LIU HY, FENG B, WANG J, et al. Effect of gastrodin on the depression-like behaviors and the expression of inflammatory factors in mice. Central South Pharmacy, 2018, 16(2): 166–170.

[141] ZHANG RG, PENG ZW, WANG HH, et al. Gastrodin ameliorates depressive-like behaviors and up-regulates the expression of BDNF in the hippocampus and hippocampal-derived astrocyte of rats. Neurochemical Research, 2014, 39(1): 172–179.

[142] AN L, YANG JC, WANG LB, et al. Study on the antidepressant effect of oligosaccharide from chrysanthemum tuber. Military Medicine, 2016, 40(1): 79–80.

[143] XU DF, MI WF, ZHANG SZ, et al. Study on the mechanism of antidepressant effect of Morindae Officinalis Radix oligosaccharides. The Chinese Journal of Clinical Pharmacology, 2015, 31(15): 1539–1542.

[144] CAI B, CUI CB, CHEN YH, et al. Antidepressant effect of inulin-type oligosaccharides from *Morindae officinalis* How in mice. Chinese Journal of Pharmacology and Toxicology, 1996, (2): 30–33.

[145] LIU P, WANG DX, GUO DH, et al. Antidepressant effect of 3′, 6-disinapoyl sucrose from *Polygala tenuifolia* Willd in pharmacological depression model. Chinese Pharmaceutical Journal, 2008, (18): 1391–1394.

[146] WANG HL. Pharmacodynamic studies of *Hippophae rhamnoides* L. on nervous system related diseases. Changchun: Jilin University, 2019.

[147] MA Q, PU Y, YUAN WQ, et al. Antidepressant effect of lentinan in chronically stressed mice and its possible mechanism. Cellular & Molecular Immunology, 2015, 31(3): 329–333.

[148] ZHANG TZ, YANGSH, DU J, et al. Antidepressant-like effects of cordycepin in a mice model of chronic unpredictable mild stress. Hindawi Publishing Corporation, 2014, 2014: 1–9.

[149] LIAO HB, LIU P, HU Y, et al. Antidepressant-like effects of piperine and its neuro protective mechanism. China Journal of Chinese Materia Medica, 2009, 34(12): 1562–1565.

[150] LI S, WANG C, WANG M, et al. Antidepressant like effects of

piperine in chronic mild stress treated mice and its possible mechanisms. Life Sciences, 2007, 80(15): 1373–1381.

[151] LIAO HB, LIU P, HU Y,et al. Antidepressant effects of piperine and its neuroprotective mechanism in rats. Journal of Chinese Integrative Medicine, 2009, 7(7): 667–670.

[152] LI S, WANG C, LI W, et al. Antidepressant-like effects of piperine and its derivative, antiepilepsirine. Journal of Asian Natural Products Rerearch, 2010, 9(3-5): 421–430.

[153] KIM SJ, LEE L, KIM JH, et al. Antidepressant-like effects of Lycii Radicis Cortex and betaine in the forced swimming test in rats. Biomolecules & Therapeutics, 2013, 21(1): 79–83.

[154] JIANG B, HUANG C, CHEN XF, et al. Tetramethylpyrazine produces antidepressant-like effects in mice through promotion of BDNF signaling pathway. International Journal of Neuropsychopharmacology, 2015, 18(8): 1–13.

[155] FU S, WANG J, HAO C, et al. Tetramethylpyrazine ameliorates depression by inhibiting TLR4-NLRP3 inflammasome signal pathway in mice. Psychopharmacology, 2019, 236(7): 2173–2185.

[156] XIE G. Study on the antidepressant effects and mechanisms of tea purine alkaloids. Jinan: Jinan University, 2010.

[157] PENG B, LIU ZH, LIN Y, et al. The ameliorative effect of L-theanine on chronic unpredictable mild stress-induced depression in rats. Journal of Tea Science, 2014, 34(4): 381–386.

[158] WU Y, SHEN M, LU W, et al. L-theanine improves depressive behavioral deficits by suppressing microglial activation in a rat model of chronic unpredictable mild stress. International Journal of Clinical and Experimental Medicine, 2017, 10(3): 4809–4818.

[159] YANG ZY. Effect of orange essential oil on the relieving of depression in mice. Wuhan: Huazhong Agricultural University, 2017.

[160] IP FCF, NG YP, AN HJ, et al. Cycloastragenol is a potent telomerase activator in neuronal cells: implications for depression management. Neurosignals, 2014, 22(1): 52–63.

[161] ITO S, NITTA Y, FUKUMITSU H, et al. Antidepressant-like activity of 10-hydroxy-trans-2-decenoic acid, a unique unsaturated fatty acid of royal jelly, in stress-inducible depression-like mouse model. Journal of Evidence-Based Complementary and Alternative Medicine, 2011, 2012: 1–6.

[162] YAO Y, HUANG HY, YANG YX, et al. Cinnamic aldehyde treatment alleviates chronic unexpected stress-induced depressive-like behaviors via targeting cyclooxygenase-2 in mid-aged rats. Journal of Ethnopharmacology, 2015, 162: 97–103.

[163] SUBARNAS A, TADANO T, NAKAHATA N, et al. A possible mechanism of antidepresant activity of beta-amyrin palmitate isolated from Lobelia Inflata leaves in the forced swimming test. Pergamon, 1993, 52(3): 289–296.

[164] DHINGRA D, BANSAL Y. Antidepressant-like activity of beta-carotene in unstressed and chronic unpredictable mild stressed mice. Journal of Functional Foods, 2014, 7: 425–434.

[165] TANG XY, XIE GZ, ZHANG SH, er al. Deveopment and application of “ one root of medicine and food ”. Modern Chinese Medicine, 2022, 22(9): 1428–1433.

[166] LIU HL, WEI FX, QIN XM, et al. Research progress in combination applications of antidepressant drugs. China Journal of Chinese Materia Medica, 2020, 45(16): 3776–3783.

[167] PLACKETT B. The vicious cycle of depression and obesity. Nature, 2022, 608(7924): S42–S43.

功能性食品及药食同源产品中抗抑郁活性成分及其作用机制

叶恬[a], 徐梦涛[a], 方景鹏[a], 吴沁璇[b], 邹小艳[b], 颜昉芩[c], 卿志星[a*]

a. 湖南农业大学中兽药湖南省重点实验室, 湖南 长沙 410128, 中国
b. 长沙医学院药学系, 湖南 长沙 410219, 中国
c. 郑州大学化学学院, 河南 郑州 450001, 中国

【摘要】目的 本研究通过总结归纳功能性食品及药食同源产品中活性成分的抗抑郁作用及其机制，以期为抑郁症的治疗提供一种新思路。**方法** 通过 PubMed, 谷歌学术，Web of Science 及中国知网数据库收集与功能性食品或食品同源产品抗抑郁相关的文献，检索时限为 1996 年 9 月 25 日至 2022 年 9 月 5 日，系统总结与分析其抗抑郁活性成分及作用机制。**结果** 研究最终纳入文献 146 篇，共计 67 种植物来源的功能性食品或药食同源产品、32 种具有抗抑郁活性的提取物（含 8 种黄酮提取物）和 87 种抗抑郁活性成分。87 种抗抑郁活性成份包括萜类 7 种，皂苷类 22 种，黄酮类 15 种，苯丙素类 11 种，酚类 7 种，糖类 6 种，生物碱类 8 种，其他类 11 种。**结论** 本综述对功能性食品及药食同源产品中抗抑郁活性成分及作用机制进行总结与分析，为新型抗抑郁药物的开发提供了新的视野，同时也为抑郁症患者的治疗提供一种潜在替代治疗方案。

【关键词】 抗抑郁；药食同源；功能性食品；提取物；活性成分；中医药