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Natural Compounds and Depressive Disorder: A Review Highlighting Botanical Sources and Reaction Mechanisms

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ABSTRACT

Depressive disorder is a typical mental illness characterized by depressed mood and anhedonia, with a great burden to patients and society. Currently, only a small minority of medicines are efficient in the clinic with high prices and various adverse reactions, including sleep disorders and gastrointestinal reactions. To develop new antidepressants, pharmacists have gradually turned their attention to phytochemicals, especially those from traditional Chinese medicine (TCM). Natural products could be good candidates for developing effective drugs and valid therapeutic strategies. In this article, we reviewed more than 20 natural compounds from TCMs with protective action against the depressive disorder, and their reaction mechanisms were reviewed from four aspects: reversing neurotransmitter imbalance, maintaining neuroendocrine homeostasis, alleviating synaptic plasticity dysfunction, and inhibiting neuroinflammation.

Abbreviations: TCM: Traditional Chinese Medicine; NR3C1: Nuclear Receptor Subfamily 3 Group C Member 1; GRIN2A: Glutamate Ionotropic Receptor NMDA Type Subunit 2A; CUMS: Chronic Unpredictable Mild Stress; SDS: Social Defeat Stress; LH: Learned Helplessness; CRS: Chronic Restraint Stress; HPA: Hypothalamic-Pituitary-Adrenal; OVX: Ovariectomized; OB: Olfactory Bulbectomy; MCAO: Middle Cerebral Artery Occlusion; TCA: Tricyclic Antidepressants; SSRI: Selective Serotonin Reuptake Inhibitors; NSMRI: Selective Monoamine Reuptake Inhibitors; MAOI: Monoamine Oxidase Inhibitors 5-HT: 5-Hydroxytryptamine; NE: Norepinephrine; MAOI: Monoamine Oxidase Inhibitor; GluR: 5-HIAA Ionotropic Glutamate Receptors; mGluR: Metabotropic Glutamate Receptors; NMDAR: N-Methyl-D-Aspartate Receptor; AMPAR: A - Amino-3-Hydroxy-5-Methyl-4-Isoxazol-Propionic Acid Receptor; GABA: Gamma-Amino Butyric Acid; CCI: Chronic Constriction Injury; 4-AP: 4-Aminopyridine; M1-AChR: M1-Type Muscarinic Acetylcholine Receptors; HPT: Hypothalamic-Pituitary-Thyroid; HPG: Hypothalamicpituitary-Gonad; BBB: Blood Brain Barrier; Cx43: Connexin43; BDNF: Brain-Derived Neurotrophic Factor; TrkB: Tyrosine Kinase Receptor B; KYN: Kynurenine; DG: Dentate Gyrus; LTP: Long-Term Potentiation; NSCs: Neural Stem Cells; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; iNOS: Nitric Oxide Synthase; DHM: Dihydromyricetin; p-ERK1/2: Phosphorylated Extracellular Signal-Regulated Kinase ½; WKY: Wistar-Kyoto

Introduction

Etiology of Depressive Disorder

Depressive disorder is a recurrent serious neuropsychiatric disease, with an incidence of up to 17% [1,2]. What's more, the direct or indirect cost of the depressive disorder has reached US$2.5 trillion and is expected to exceed US$6 trillion by 2030. Approximately 1,000,000 people die of suicide every year around the world [3,4], and more than 90% of them have been diagnosed with depression or other mood disorders [5]. In general, depression brings tremendous social and economic burdens, as well as a gigantic adverse effect on social activities and family responsibilities. As a complex multifactor disease, depressive disorder is initiated and triggered by psychological, genetic, social, and biological factors. Increasing evidence shows that the occurrence and development of depression are closely related to genetic factors, and depression is a highly inherited disease, with 40% - 50% of its risk coming from genes [6]. Multiple genes such as Nuclear receptor subfamily 3 group C member 1 (NR3C1), glutamate ionotropic receptor NMDA type subunit 2A (GRIN2A), and many others are closely related to depression outcome [7,8]. Psychological factors contain abuse (including sexual, physical, or emotional), psychological neglect, exposure to violence, separation, and bereavement, and so on. Social factors, such as chronic health problems, exposure to violence, financial insecurity, are strongly associated with the risk of developing depressive disorder. Biologically speaking, periodic changes of hormones and long-term health problems can also contribute to the occurrence of depression, such as postpartum depression and diabetic depression.

Animal Models of Depressive Disorder

Due to the complex pathogenic factors and the high comorbidity rate with other mental diseases (such as anxiety, phobia, schizophrenia, etc.), it is difficult to maintain a strict boundary between depression and other mental diseases, and the animal models of depression are essential to understand the pathological mechanism [9]. Presently, rats (Sprague-Dawley rats, Wistar rats), mice (C57BL/6 mice, ICR mice, Kunming mice), non-human primates (rhesus monkeys, cynomolgus monkeys, etc.), zebrafish, tree shrew are common model animals for the preclinical study of depression. In the aspect of animal modeling, stress exposure is the most common molding method, because it can simulate the clinical disease process of humans to the greatest extent, including chronic unpredictable mild stress (CUMS) [10,11], social defeat stress(SDS) [11,12], learned helplessness (LH), chronic restraint stress (CRS). On the other hand, some depressive animal models were set up guided by the corresponding hypothesis, such as injection of lipopolysaccharide (inducing inflammation) [13], corticosterone (destructing HPA axis) [14,15], and reserpine (exhausting monoamine transmitter) [16,17]. Besides, surgical models are also good choices to establish a depression model, including ovariectomized (OVX), olfactory bulbectomy (OB), and middle cerebral artery occlusion (MCAO). Despite multiple modeling methods, CUMS is the most classical and widespread one.

Intervention in Depressive Disorder

Presently, the commonly prescribed antidepressants have been divided into four categories, including tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), non-selective monoamine reuptake inhibitors (NSMRI), and monoamine oxidase inhibitors (MAOI) [18]. However, conventional antidepressants lack efficacy in many patients (treatment-resistant depression), and combined medication (multitherapy) and several weeks were required to produce a therapeutic response in about 50% of depression cases [19,20]. Besides, there is also increasing evidence in terms of serious side effects of antidepressants, such as cognitive impairments, arrhythmias, sleep disorders, and gastrointestinal reactions. For example, fluoxetine is one of the most common antidepressants worldwide, while it also induces many side effects such as hepatotoxicity and gastrointestinal reaction [22]. Thus, these disadvantages of antidepressants may limit clinical use and are not directly conducive to the treatment of depression. Psychotherapy is a common treatment program for depression, but it does not demonstrate outstanding superiority compared with control [23]. Likewise, Cochrane reviews that the evidence of other alternative therapies, such as acupuncture and exercise, are short of persuasiveness and convincing [24,25]. Therefore, current researchers are devoted to the search and development of novel effective drugs with high efficacy and low side-effects during the past two decades [26,27]. Traditional Chinese medicine has unique advantages in prolonging the human life span, improving the quality of life, and preventing and treating chronic diseases, including diabetes, cancer, and depressive disorder.

Materials and Methods

We searched the relevant experimental articles published from October 2014 to July 2021 in the PUBMED database to clarify the antidepressant effects of natural compounds. Our search statement is designed according to the following criteria: the search language contains relevant keywords such as 'depressive disorder' and 'natural product' or compounds category, including alkaloids, flavonoids, polyphenols, phenylpropanoids, polyphenols, and quinones. After completing the preliminary search, duplicated or non-English articles, as well as studies involving natural products of multiple compounds such as extracts were deleted, and the literature on single compounds was retained so that we could completely comprehend how each natural compound exerts antidepressant effects and their potential mechanism.

Results

Natural Compounds that Restore Neurotransmitter Imbalance

Neurotransmitters are messengers of information exchange between neurons or between neurons and effector cells such as muscle cells, glandular cells, etc., including monoamines (norepinephrine, dopamine, and serotonin), amino acids (excitatory transmitters such as glutamic acid and aspartic acid; inhibitory transmitters such as γ-aminobutyric acid, glycine, and taurine), choline (acetylcholine) and others, such as neuropeptides and purines [28]. In this section, plant chemicals and/or extracts are listed according to their impacts on neurotransmitters. Their chemical structures, antidepressant activities, and action on restoring neurotransmitter imbalance in animal models of depression are discussed.

Natural Compounds Regulating Monoamine Neurotransmitters and Related Receptors: Among all of the neurotransmitters, monoamine neurotransmitters are most closely related to depression, and valid antidepressant drugs are mainly designed to target the monoamine neurotransmitter system, including the serotonergic and noradrenergic systems. Currently, the monoamine transmitter hypothesis believes that the concentration of brain neurotransmitters in the synaptic gap is relatively or absolutely insufficient, which will lead to overall mental activity and mental function in a comprehensive state of depression [29]. Clinical studies have found that 5-hydroxytryptamine (5-HT) and norepinephrine (NE) are insufficient in the brain of depressed patients, while antidepressants can exert effects by inhibiting the reuptake of these two neurotransmitters and increasing the concentration of transmitters in the synaptic gap [30,31].

Ferulic Acid: Ferulic acid, or 4-hydroxy-3-methoxy-cinnamic acid, is derived from Umbelliferae family TCM plants, such as *Ferulae Resina* (e'wei, 阿魏), *Angelicae Sinensis Radix* (danggui, 当归), *Aconiti Radix* (chuanxiong, 川芎), *Cimicifugae Rhizoma* (shengma, 升麻), and *Ziziphi Spinosae Semen* (suanzaoren, 酸枣仁). As a polyphenol compound, ferulic acid has good blood-brain barrier permeability [32]. Many studies have shown that ferulic acid may be an MAOI antidepressant, suggesting that ferulic acid selectively increases the levels of serotonin and norepinephrine in the various brain to alleviate depression [33,34]. Moreover, the inhibitors of 5-HT1A/5-HT2A receptors can clear up the antidepressant activity of ferulic acid [35]. Furthermore, Li G, et al. [36] performed that the administration of ferulic acid exerts obvious antidepressant effects by reducing MAO-A activity and 5-HIAA content, which suggested that ferulic acid, combined with a low dose of piperine, may be a potential therapeutic method of depression with high efficacy and low side effects.

Naringenin: Naringenin is a special flavonoid widely distributed in various Chinese Medicine for antidepressants, such as *Menthea haplocalycis herba* (bohe, 薄荷) and *Auranrii fractus* (zhiqiao, 枳壳). Compared with other flavonoids, it is more easily to be absorbed by the gastrointestinal tract, with high bioavailability and high safety dose [37,38]. Mounting evidence shows that naringenin is a potential antidepressant [39-44]. On the one hand, it can increase the 5-HT level by inhibiting MAO [45] or regulating the metabolic process of tryptophan [39,41]. Another, it exerts a neuroprotective role through the sonic hedgehog-Gli1 signaling pathway and restores alterations in the kynurenine (KYN) pathway via its antioxidant and anti-inflammatory potential [40,42].

Umbelliferone: Umbelliferone, or 7-hydroxycoumarin, is one of the coumarin derivatives. Many effects have been documented for this compound ranging from anti-oxidation, anti-inflammatory, and neuroprotection. As for depression, this compound can significantly improve CUMS-induced depressive behaviors, including lack of pleasure and prolonged immobility. It can inhibit the activity of MAO and lower the elimination of 5-HT [46]. Interestingly, many of its derivatives also are good MAO inhibitors [47]. Besides, umbelliferone can inhibit neuronal apoptosis via modulating the ROCK/Akt pathway or GSK-3β/PI3K/Akt pathway to treating depression [48,49].

Chrysin: Chrysin is a kind of flavonoid extracted from the plant of *Oroxyli semen* (muhudie, 木蝴蝶) or propolis, with extensive pharmacological activity, including strong neuroprotective and anti-inflammation effects [50]. And it is potent for depression caused by different reasons, such as ovariectomy, hypothyroidism, CUMS, traumatic brain injury, and olfactory bulbectomy [50-58]. Chrysin can not only increase the level of BDNF [51,57] and other neurotrophic factors, but also regulate the level of 5-HT and its production and metabolism [54,55,57,58].

Natural Compounds that Regulate Amino Acid Neurotransmitters and their Receptors: Amino acid neurotransmitters include excitatory transmitters (e.g. glutamate and aspartic acid) and inhibitory transmitters (e.g. γ-aminobutyric acid, glycine, and taurine). Growing evidence demonstrates that glutamatergic transmission may be the critical cause of depression occurrence, though the imbalance of monoamine neurotransmitters is the classic pathogenesis of depression [59]. Both clinical and preclinical results show that depression is closely related to the increase in glutamate concentration [60]. The receptors of glutamate are divided into ionotropic glutamate receptors (GluR) and metabotropic glutamate receptors (mGluR). The former includes N-methyl-D-aspartate receptor (NMDAR), α - amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid receptor (AMPAR), and kainate receptor family, while the latter belongs

to G protein-coupled receptors and involves eight subtypes, mGluR1~8. Previous studies have indicated that NMDAR, AMPAR, and mGluR (1/2/3/5) are closely related to depression [61,62]. However, lowering inhibitory transmitters GABA, also known as γ-aminobutyric acid, is associated with depression, and GABA regulates local neural circuits including norepinephrine, dopamine, and serotonin neurons [59,63]. Therefore, the balance between glutamate and GABA is considered one of the key points in the pathogenesis of depression.

Curcumin: Curcumin is a polyphenol component extracted from *Zingiberaceae* and *Araceae* family, and the typical TCMs include *Wenyujin Rhizoma Concisum* (jianghuang, 姜黄), *Curcumae* Radix (yujin, 郁金), and *Curcumae Rhizzoma* (e'zhu, 莪术). Multiple functions have been reported for this agent, including lipid regulation, inflammation inhibition, and tumor suppression. As for depression, this compound can normalize the depressive behaviors in lipopolysaccharide-induced and chronic constriction injury (CCI) model mice [64-66]. And above ant depression was greatly eliminated by GABA receptor A antagonist bicuculline, but only partly abrogated by 5-HT receptor 1A antagonist [65]. Similarly, Ro25-6981 (GluN2B antagonist) was found to prevent the pharmacodynamics function of curcumin in FST [64]. From another perspective, curcumin can inhibit glutamate release from synaptosomes induced by 4-aminopyridine (4-AP), a K^+ channel blocker, which can be completely abolished by fluoxetine, a clinically effective antidepressant [67]. Thus, the antidepressant effect of curcumin may be mediated, at least in part, by regulating the balance between glutamate and GABA.

Natural Compounds that Regulate Cholinergic Neurotransmitters and their Receptors: The cholinergic system plays a significant role in regulating various CNS functions, including arousal, attention, cognition, and memory, and the abnormality of the cholinergic system is associated with depression. Although the role of the cholinergic system in the pathogenesis of depression is not as widely accepted as the monoamine hypothesis, it has been proposed decades ago. Recent studies have shown that increasing the activity of the cholinergic system shortly before stress induction can affect the ability to cope with forthcoming stress, bringing about depression-like conditions [68,69].

Scopolamine: Scopolamine, separated from nightshade family plant *Dature Stramonium Datura L*, is a nonselective muscarinic antagonist, especially for M1-type muscarinic acetylcholine receptors (M1-AChR); and its main effects are used to treat motion sickness and nausea, but growing studies have revealed that scopolamine posts a rapid antidepressant activity in humans and animals, and maybe a promising antidepressant agent or adjuvant. However, its antidepressant activity can be eliminated by M1-AchR knockout [70], AZD8055 (an orally-bioavailable mTOR inhibitor) [71], AMPT (a tyrosine hydroxylase inhibitor) [72], NBQX (an inhibitor of AMPAR) [73], or VGLUT1 knockdown [74]. Overall, these results indicate that although scopolamine is a muscarinic antagonist, its antidepressant effect in animal depression models is related to not only the cholinergic system but also to noradrenergic and glutamic acid systems and the mTOR pathway.

Natural Compounds that Maintain Neuroendocrine Homeostasis

The endocrine system is another important functional regulation system besides the nervous system, and the main endocrine organs include the pituitary gland, thyroid gland, adrenal gland, islet of the pancreas, and gonad. Especially, the hypothalamus cannot only regulate nerve function, but also measure endocrine function, and there are three important neuroendocrine axes, including the HPA axis, HPT axis, and HPG axis. Among these, the HPA axis is an important neuroendocrine system for the human body to cope with stress. When individuals are faced with stressors, they can increase hormone levels in a series of ways, causing the human body to produce a stress response.

Ginsenoside Rg1: Ginsenoside Rg1 is one of the most active components in *ginseng radix et rhizoma* (renshen, 人参), which has a variety of biological activities, including promoting neurogenesis and neural plasticity, enhancing learn and memory, and improving immunity. Therefore, this compound may have great potential in the treatment of depression. Several studies have proved that ginsenoside Rg1 significantly alleviates depressive behaviors induced by CUMS, CSDS, or corticosterone [75-79]. It has been shown that ginsenoside Rg1 can protect the function of gap junction to repair the integrity of blood-brain barrier (BBB) and connexin43 (Cx43) is the key sensitive target [80-82]. Moreover, it also can reduce dendritic spine atrophy and modulate the homeostasis of the HPA and HPG axis [83].

Puerarin: Puerarin is a kind of isoflavone derivative isolated from TCM, *Pueraria lobata* (gegen, 葛根), and is also the main pharmacological component. Its main effects are to dilate blood vessels and improve microcirculation, so it is often used in the treatment of hypertension and coronary artery disease [84]. However, recent researchers have found puerarin may be a potential antidepressant, due to its neurotrophic and estrogen-like effects [85-87]. Of note, it has been reported that puerarin shows a significant antidepressant effect on ovariectomized ICR mice, including behavioral remission and corticosterone reduction [87]. Further, puerarin also dose-dependently normalized the downregulated transcription of estrogen receptor (Erβ and Erα) and BDNF mRNAs [87]. On the other hand, puerarin plays a biological role in the synthesis of allopregnanolone in the brain [88]. In summary, puerarin exerts antidepressant effects directly through its estrogen-like effect, or indirectly through promoting the biosynthesis of estrogen.

Hyperforin and Hyperoside: *Hypericum perforatum* (guanyejinsitao, 贯叶金丝桃), namely St John's wort, is a classic antidepressant plant drug. Hyperforin and hyperoside are its main active components, and even have been regarded as the quality control index. Due to their significant efficacy and small side effects, they have become the first choice for the treatment of depression in Europe and the United State. Previous evidence has shown that the two compounds can inhibit the activity of MAO and the synaptosomal reuptake of monoamine [89]. However, recent studies show that hyperforin can activate TRPC6-mediated currents and Ca^{2+} transients to modulate synaptic plasticity in rat PC12 cells, and change BDNF and zinc levels in mice exposed to CUMS to exert significant antidepressant-like activity [90,91]. Similarly, hyperoside protects rats from CMS-induced learning and memory deficits, while these effects could be prevented by K252a, an inhibitor of the BDNF receptor tyrosine kinase receptor B (TrkB) [92]. Therefore, hyperforin and hyperoside can recovery the synaptic function to treat depressive disorder.

Hesperidin: Hesperidin is the main active component of TCM from the Rutaceae family, including *Citri reticulatae pericarpium* (chenpi, 陈皮), *Auranrii fractus* (zhiqiao, 枳壳), and *Citri sarcodactylis fructus* (foshou, 佛手), which are related to soothing the liver and relieving depression. Hesperidin has been reported to exhibit a beneficial effect on various depressive animals, and alleviating neuroinflammation may be the key mechanism of efficacy [92,93]. It has been reported that this phytochemical could not only inhibit the increase of KYN level in the prefrontal cortex of CSDs rats, but also antagonize the downregulation of miRNA-132 expression in lipopolysaccharide-induced depression mice [94,95]. Moreover, hesperidin reduces inflammatory cytokine levels by modulating the HMGB1/RAGE/NF-κB pathway and the BDNF/TrkB pathway both *in vivo* and *in vitro* [96]. Thus, hesperidin may be a potential antidepressant candidate.

Paeoniflorin: Paeoniflorin, exacted from Paeoniae root, is the principal bioactive ingredient of *Paeoniae radix rubra* (chishao, 赤芍) and *Paeoniae radix alba* (baishao, 白芍). Due to its low toxicity, there is no obvious adverse reaction under normal conditions. A large number of studies have proved that paeoniflorin has many pharmacological effects, including antidepressants, analgesics, liver protection, nerve protection, and immune regulation. Regarding depression treatment, paeoniflorin has a very significant therapeutic effect. This chemistry can promote neurogenesis in the hippocampal dentate gyrus (DG) and attenuate impairment of long-term potentiation (LTP) in hippocampal CA1 of animals subjected to CUMS [97-99]. Mechanically, the activation of the ERK/CREB pathway may be the internal reason for its antidepressant effect. On the other hand, paeoniflorin can also play a protective role in neurons through calcium antagonism [100,101].

Natural Compounds that Relieve Neurological and Synaptic Dysfunction

Synapse is the basic structure between neurons for information transmission and processing. Synaptic plasticity refers to the adaptive changes of the brain to stimulation, including structural and functional changes, which are manifested in the increase or decrease of the synaptic number, the change of synaptic morphology, and the adjustment of synaptic function. Peripheral inflammation and synaptic abnormalities are thought to directly or indirectly induce brain functional abnormalities contributing to depression [102,103], and the change of synaptic plasticity has become one of the key indicators in the treatment of depression.

Asiaticoside: Asiaticoside, the main active ingredient in *Centellae herba* (jixuecao, 积雪草), has many pharmacological activities, including regulating immunization, anti-inflammatory and promoting wound healing [104]. Luo, L et al. [105] found that asiaticoside poses a significant antidepressant action in CUMS-exposed mice through activating BDNF signaling in the hippocampus, which could be totally eliminated by K252a, a BDNF receptor inhibitor. Furthermore, asiaticoside was able to reverse the inflammation and the PKA/pCREB/BDNF signaling pathway to play an antidepressant effect [106].

Harmine: Harmine, a confirmed MAO inhibitor, is a natural β-carboline alkaloid extracted from *Peganum harmala L* (luotuopeng, 骆驼蓬) used by Mongolian doctors and is considered a potential antidepressant. It was reported that harmine treatment (20mg/kg) decreases the immobility in TST and FST, and increases the sucrose intake in SPT, and prevents reductions of BDNF, GLT-1, and GFAP in the hippocampus induced by CUS [107]. Besides, its antidepressant effects were able to eliminate by l-Alpha-Aminoadipic Acid, gliotoxin specific for astrocytes, which means harmine was an effective therapeutic agent via the restoration of astrocytic dysfunctions [108]. However, a study certified that harmine (15 mg/kg, i.p.) has no effects on RSD-induced acute depressive behavior, or even caused some unpredicted side effects, such as severe weight loss and reduced locomotion on open field tests [109].

Silymarin: Silymarin is a flavonoid mixture composed of silybin, isosilybim, silydianin and silychristin, which are extracted from *Silybi fructus* (shuifeij, 水飞蓟). Concerning antidepressants, silymarin has a distinct effect on olfactory bulbectomized (OBX) mice and CUMS mice [110,111]. These compounds were also shown to improve the proliferation of neural stem cells (NSCs), promote phosphorylation of ERK and CREB, as well as modulate the expression of BDNF and TrkB, while the above efficacy of silibinin is neutralized by TrkB antagonist, GNF5837 [112].

Baicalin: Baicalin, the main active component of *Scutellariae radix* (huangqin, 黄芩), has a variety of pharmacological effects, such as antibacterial, diuretic, anti-inflammatory, cholesterol lowering, antithrombotic, and so on [113]. Meanwhile, generous evidence shows that baicalin has a good therapeutic effect on depressive animals. On CUMS mice, baicalin can regulate the NMDAR/NR2B-ERK1/2-related pathway to ameliorate behavioral performance and reduce cytokines levels [114]. Differently, this compound can reduce the serum level of corticosterone on depression mice induced by 21-day corticosterone injection, and increase the expression of BDNF in the hippocampus by GR/SGK-1/BDNF pathway [115]. Other, baicalin exert obvious antidepressant activity on rat induced by OBX, and its core mechanism is related to anti-oxidation and anti apoptosis [116].

Paeonol: Paeonol is an effective component extracted from the *Moutan cortex* (mudanpi, 牡丹皮), which has prominent effects on analgesia, anti-inflammation, antipyretic and anti-allergic reactions. This agent has been shown to attenuate lipopolysaccharide-induced depressive-like behavior in mice [117]. Furthermore, it also affects CUMS-induced rats. After Paeonol application for 4 weeks, the length and density of dendritic spines in hippocampal CA1 and dentate gyrus (DG) were considerably increased, while the expression of Rac1/RhoA was upregulated [118]. These results suggested that paeonol could restore synaptic plasticity through the BDNF-Rac1/RhoA pathway to an anti-depressant.

Neuroinflammation Reaction

Depression is accompanied by the up-regulation of inflammatory factors, such as IL-1β, IL-6 and TNF-α. Meanwhile, anti-inflammatory agents such as non-steroidal anti-inflammatory drugs (NSAIDs), inflammatory factor inhibitors, and statins can improve the behavioral score of depressive patients by improving neuroinflammation [119,120]. Additionally, some inflammatory factors, such as CRP, IL-6, and TNF-α, can be used as biomarkers of depression [121]. Microglia and astrocytes are also found to be activated in the brain of depressed mice [122]. Therefore, neuroinflammation may be the key pathogenesis of depressive disorder. In this section, we discuss the compounds and/or extracts that exert anti-neuroinflammation activities in microglia and/or depressive animal models.

Sinomenine: Sinomenine is a monomeric alkaloid that can be extracted from Chinese traditional medicine *Sinomenii caulis* (qingfengteng, 青风藤). Multifold effects have been reported for this chemistry ranging from pain relief, inflammatory inhibition, and immunologic suppression [123]. Sinomenine has also be shown a significant anti-depressant effect on depressive animals treated by CSDS or CUMS [124,125]. It can reduce the levels of IL-1β, IL-6, and TNF-α in the hippocampus of mice, by preventing NF-κB pathway and NLRP3 inflammasome activation. Therefore, sinomenine may be a promising and effective drug for depression.

Berberine: Berberine is the main component of the Chinese herb *Coptidis rhizoma* (huanglian, 黄连) with many pharmacological effects, such as anti-inflammatory, antiviral, anti-arrhythmia and antihypertension [126]. Differently, berberine has been documented to exhibit a favorable effect on neuroinflammation suppression [127]. It can decline the expression of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α), and inhibit microglial activation and NF-κB signaling pathway, including IκB kinase (IKK)α, IKKβ and nitric oxide synthase (iNOS), in the hippocampus. Moreover, another recent study shows that oral administration of berberine (150 mg/kg) could increase consumption of sugar water in SPT, upregulate the expression of BDNF, GR, CREB, and NADH dehydrogenase, such as Ndufb (4, 5, 6), Ndufa (6, 7), and Ndufs4, et.al., which suggests that berberine is a potential antidepressant via ameliorating mitochondrial energy [128].

Dihydromyricetin: Dihydromyricetin (DHM), one type of flavonoid natural product isolated from *Semen hoveniae* (zhijuzi, 枳椇子), has a rapid antidepressant-like effect by activating the ERK1/2-CREB pathway. Ren Z, et al. [129] have found seven days of DHM treatment declined immobility time in the TST and FST both in normal mice and the lipopolysaccharide-induced acute depressive mice, and increased glycogen synthase kinase-3 beta (GSK-3β) phosphorylation, with the increase of BDNF expression, both *in vivo* and *in vitro*. Additionally, Guan S, et al. [130] studied that DHM could relieve diabetic depressive disorder, as indicated by a series of behavioral tests, such as SPT, FST, and OFT, and the mechanism may be through reducing the expression of the P2X7 receptor which is a member of the ATP-gated ion channel family, phosphorylated extracellular signal-regulated kinase 1/2(p-ERK1/2), TNF-α, and IL-1ß in the DRGs, spinal cord, and hippocampus.

Icariin: Icariin, a flavonoid isolated from the Chinese herb *Epimedii folium* (yinyanghuo, 淫羊藿), can penetrate the blood-brain barrier to play an anti-inflammatory and antioxidant role in CNS [131]. Moreover, it has been shown to decline depressive disorder in CMS-treated animals [132]. This decline covered inflammatory mediators (TNF-α, IL-1β, and NF-κB) and oxidative-nitrosative stress markers (MDA, SOD, CAT, and iNOS) in CMS rats' hippocampus. Importantly, icariin can inhibit microglial activation and regulate the NLRP3-inflammasome/caspase-1/IL-1β axis [133]. On the other hand, icariin also can regulate the expression of mGluR1, mGluR5, and EAAT2 in the hippocampus to ameliorate depression induced by prenatal restraint stress [134].

Apigenin: Apigenin is widely distributed in tropical vegetables and fruits, especially in celery or *Apii herba* (hanqin, 旱芹). Many studies [135,136] have reported that apigenin relieved depressive

behavior induced by CUMS in rats. This fraction sharply lessens the production of IL-1β and IL-18, with balancing oxidation markers (GSH and MDA) in PFC [137]. Particularly, apigenin can up-regulate the expression of PPARγ to reduce NLRP3 inflammasome, and its antidepressant effect can be neutralized by GW9662, a selective PPARγ inhibitor [137], which suggests that PPARγ may be the crucial target for apigenin to exert antidepressant efficiency.

Fisetin: Fisetin, a type of small-molecule flavonoid, is abundantly found in fruits and vegetables, with multiple roles including antitumor, hepatoprotective, and antidepressant [138]. Upon depression treatment, fisetin exerted a well-being response to the lipopolysaccharide-induced model by neuroprotective and anti-inflammation effects, except by inhibiting monoamine oxidase (MAO) [139,140]. It was able to reverse the expression of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) and reduce iNOS mRNA expression by modulating the NF-κB pathway [140].

Resveratrol: Resveratrol is a natural phytoalexin, widely present in grapes, peanuts, and *Veratrum nigrum* (huzhang, 虎杖) [141]. Mounting evidence shows that resveratrol possesses various bioactivities, including cancer suppression, inflammation inhibition, oxidation-reduction, and many others. For depression, resveratrol has been reported to prevent depressive disorder depression in animals triggered by SD or CUMS [142,143]. The prevention was ascribed to a decrease of pro-inflammation cytokines (TNF-α, IL-Iβ, GM-CSF, NF-κB) in peripheral and central positions, including the spleen, hippocampus, and locus coeruleus. El-Fattah AAA, et al. [143] found that resveratrol can reveal depression-like phenotypes of depression rats induced by CUMS, which was relevant to the suppression of MDA and increase of GSH in the hippocampus. Likewise, chronic treatment of resveratrol manifests an obvious antidepressant effect on Wistar-Kyoto (WKY) rats, a putative and non-induced animal model of depression [144]. Overall, resveratrol may be a potential therapeutic drug for depression.

Esculetin: Esculetin, a plant coumarin derived from the *Fraxini cortex* (qinpi, 秦皮), exhibited antidepressant-like effects on depressive mice induced by lipopolysaccharide [145,146]. It can significantly reduce pro-inflammation cytokines (IL-6, IL-1β, and TNF-α) in serum and hippocampus, attenuate the expressions of inflammation-related proteins (iNOS, COX-2, p-IKKα, p-IKKβ, p-IκBα, and p-NF-κB p65) and upregulate protein expression of BDNF and p-TrkB in the hippocampus [146].

Crocin: Crocin, derived from *Croci stigma* (xihonghua, 西红花), has been reported to ameliorate depressive behavior in mice induced by lipopolysaccharide or CORT [147,148]. The amelioration was related to a reduction in the priming of NLRP3 inflammasome and pro-inflammation cytokines (IL-1β, IL-6, IL-18, TNF-α). As well, crocin also decreases the ratio of M1/M2 of microglia and the production of cytokines (NO, TNF-α, IL-1β, ROS, iNOS, and NF-κB p65) in BV-2 microglial cells [147]. Overall, it may be useful for the treatment of depressive disorder by inhibiting the NLRP3 inflammasome and NF-κB pathway and suppressing microglial activation.

Proanthocyanidins: Proanthocyanidins are flavonoids, mostly found in grapes, apples, sorghum, cherry, and other plants [149]. The TCM of *Hippophae fructus* (shaji, 沙棘) is also one of the main sources of phytomedicine. Jiang X, et al. [150] found that proanthocyanidin reduced the immobility time of FST and TST on the lipopolysaccharide-induced depression mice. These data performed that proanthocyanidin inhibited the overexpression of iNOS, COX-2, and NF-κB in the hippocampus, PFC, and amygdala, suggested that proanthocyanidin has an effective therapeutic role on depression by modulating the NF-κB pathway [150].

Discussion

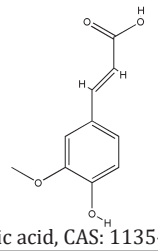
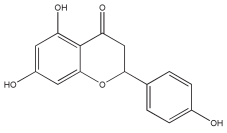
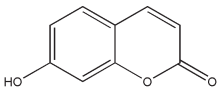
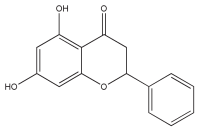
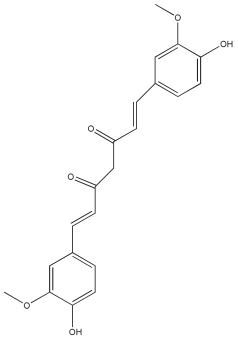
Depression is a well-known neurological disease with a wide incidence, and many various mechanisms have been proposed to explain the disease, such as dysfunction of the monoamine transmitter system, hyperactive activation of the HPA axis [151], neuroinflammation [152], and neuroplasticity [153]. Therefore, neurotransmitter balance, neuroendocrine homeostasis, neural plasticity, and neuroinflammation are the focal points of many researchers to explore the pathogenesis of depression. Take together; researchers believe that the prevention and treatment of depression involve various signaling pathways, including the nuclear factor kappa B (NF-κB) pathway, peroxisome proliferator-activated receptor gamma (PPARγ) pathway, NLRP3/caspase-1/IL-1β pathway, BDNF-ERK signaling pathway, ROCK/Akt pathway, and MEK pathway. However, existing researches are excessively scattered and lack systematicness, and it is necessary to study it systematically and intensively. Natural products come from natural creatures, which are inexhaustible treasures. At present, multiple natural products with neuropharmacological effects have been used to treat depressive disorder and depressive-like symptoms, such as phenols and flavonoids [154,155]. Hence, this article summarizes natural products with antidepressant effects. The results showed that *Umbelliferae* had the highest frequency of occurrence and may be the main source of antidepressant natural products, such as ferulic acid [33-36], umbelliferone [46-49], and apigenin [135-137].

Tracing back to its plant origin, it is found that most of its original plants are Chinese medicine with an obvious antidepressant effect. These plants include chaihu, danggui, jixuecao, qincai, and so on. Closely followed by *Rutaceae* and *Ranunculaceae*, representative compounds include naringenin [38-43, 45] and paeonol [117, 118]. The composition of traditional Chinese medicine is complex. Some compounds played antidepressant roles by regulating unique mechanisms like restoration of astrocytic dysfunctions

and suppression of microglial activation, while others modified oxidation and inflammatory reaction. It is the only way to find the best component with a significant curative effect in the complex and various components from prescription to medicine and then to compound or single component research. However, a series of profound studies, including animal studies and clinical trials, are needed to identify the latent side effects of these compounds to treat this complex disease and to further confirm the great potentiality of these compounds as candidate drugs for depressive disorder. In the aspect of animal model, stress exposure is the most common molding method, because it can simulate the clinical disease process of humans to the greatest extent, including chronic mild stress [10,11], social defeat stress [11,12]. However, they have applied various animal models, including the stress model, chemical induction model, and surgical model.

The stimulation method in the stress model includes chronic unpredictable mild stress, chronic unpredictable stress, and chronic social defeat stress, or socially defeated, which can be used to establish the depression model. In the chemical induction model, there are repetitive injections of lipopolysaccharide, corticosterone, reserpine, and 3,4-methylenedioxymethamphetamine; and the surgical model is olfactory bulbectomized. Nevertheless, the validation research is not deep enough, just like the antidepressant effect of one compound on different animal models (Table 1). If these researchers can do that, the antidepressant status of the above natural products will be consolidated and strengthened.

Table 1: Summary of the main botanical sources and pharmacological effects of natural compounds from TCMs for depressive diseases.

No.	Compound Names	Family	Main Botanical Source	Structures	Mechanisms	Ref.
1	Ferulic acid	*Umbelliferae*	*Ferulae Resina* (e'wei, 阿魏), *Angelicae Sinensis Radix* (danggui, 当归), *Aconiti Radix* (chuanxiong, 川芎), *Cimicifugae Rhizoma* (sheng-ma, 升麻), and *Ziziphi Spinosae Semen* (suanzaoren, 酸枣仁)	 Ferulic acid, CAS: 1135-24-6	inhibit MAO or the receptors of 5-HT1A/5-HT2A	[33-36]
2	Naringenin	*Rutaceae*	*Menthea haplocalycis herba* (bohe, 薄荷) and *Auranrii fractus* (zhiqiao, 枳壳)	 Naringenin, CAS: 480-41-1	increase the 5-HT level by inhibiting MAO or regulating the metabolic process of tryptophan	[37,39-45]
3	Umbelliferone	*Umbelliferae*	*Angelicae pubescentis radix* (duhuo, 独活)	 Umbelliferone, CAS: 93-35-6	inhibit the activity of MAO modulate the ROCK/Akt pathway or GSK-3β/PI3K/Akt pathway to inhibit neuronal apoptosis	[46-49]
4	Chrysin	*Bignoniaceae*	*Oroxyli semen* (muhudie, 木蝴蝶)	 Chrysin, CAS: 480-40-0	regulate the level of 5-HT and its production and metabolism increase BDNF level	[50-58]
5	Curcumin	*Zingiberaceae* and *Araceae*	*Wenyujin Rhizoma Concisum* (jianghuang, 姜黄), *Curcumae Radix* (yujin, 郁金), and *Curcumae Rhizzoma* (e'zhu, 莪术).	 Curcumin, CAS: 458-37-7	regulate the balance between glutamate and GABA via GABAA receptor and GluN2B	[64-67]

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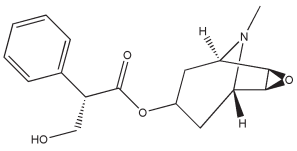
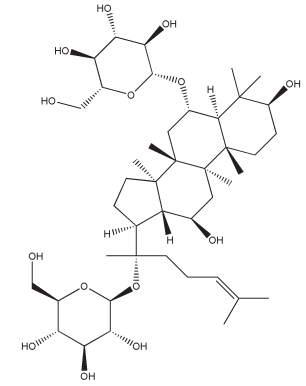
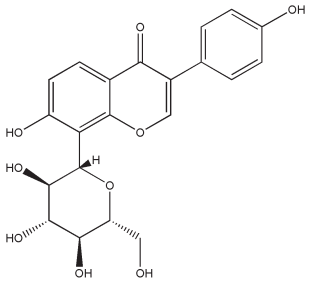
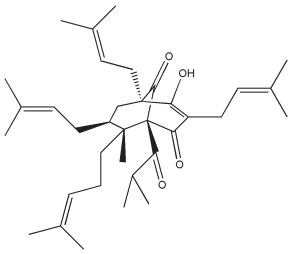
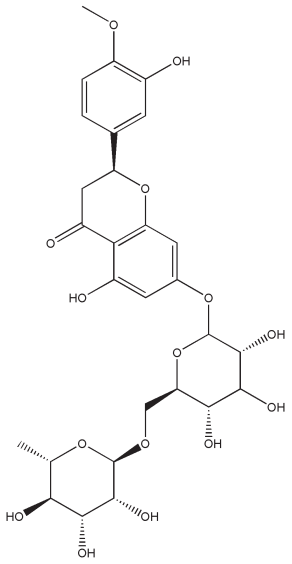
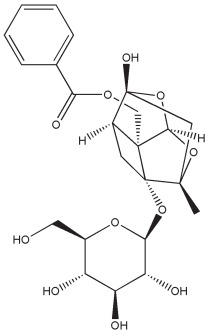
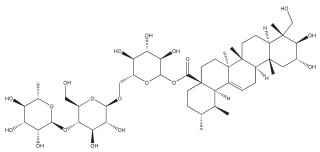
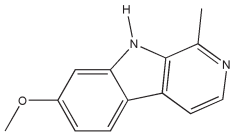
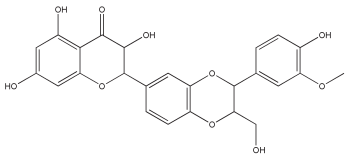
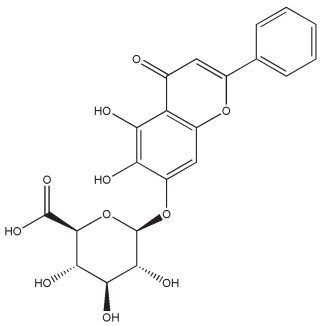
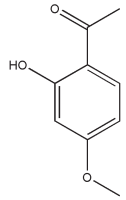
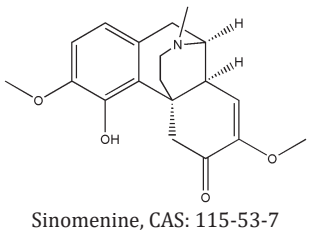
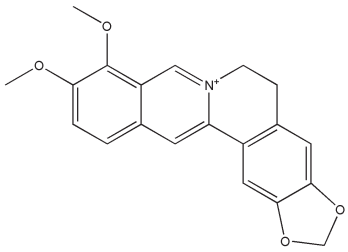
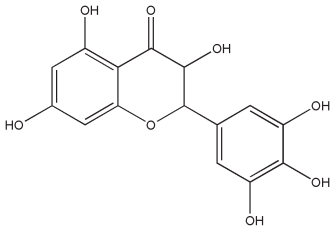
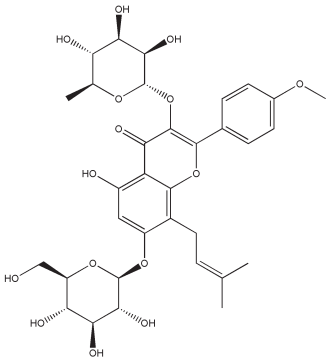
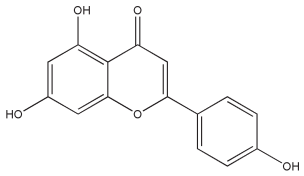
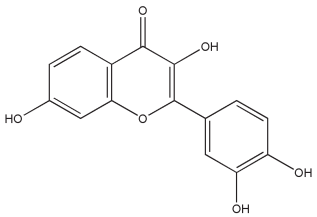
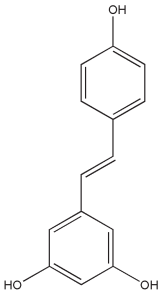
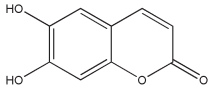
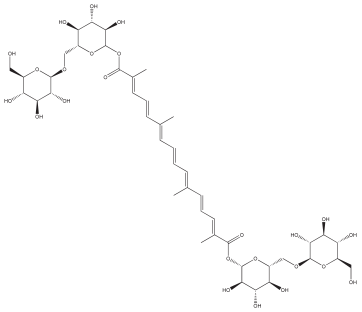
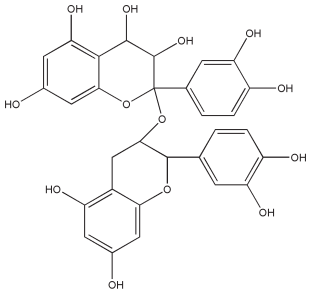
6	Scopolamine	*Solanaceae*	*Daturae flos* (yangjinhua, 洋金花)	 Scopolamine, CAS: 51-34-3	regulate the noradrenergic and glutamic acid systems and mTOR pathway	[70-74]
7	Ginsenoside Rg1	*Acanthaceae*	*Ginseng radix et rhizoma* (renshen, 人参)	 Ginsenoside Rg1, CAS: 22427-39-0	protect the function of gap junction to repair the integrity of BBB or modulate the homeostasis of the HPA and HPG axis	[75-78,80-83]
8	Puerarin	*Leguminosae*	*Pueraria lobata* (gegen, 葛根)	 Puerarin, CAS: 3681-99-0	be estrogen-like effect, or promote the biosynthesis of estrogen	[84-88]
9	Hyperforin and hyperoside	*Garciniaceae*	*Hyperici perforati herba* (guanye jinsitao, 贯叶金丝桃)	 Hyperforin, CAS: 11079-53-1	regulate the expression of BDNF/TrkB inhibit the activity of MAO and the synaptosomal reuptake of monoamine	[89-92]
10	Hesperidin	*Rutaceae*	*Citri reticulatae pericarpium* (chenpi, 陈皮), *Auranrii fractus* (zhiqiao, 枳壳), and *Citri sarcodactylis fructus* (foshou, 佛手)	 Hesperidin, CAS: 520-26-3	reduce inflammatory cytokine levels by modulating the HMGB1/RAGE/NF-κB pathway and the BDNF/TrkB pathway	[92-96]

11	Paeoniflorin	*Paeoniae*	*Paeoniae radix rubra* (chishao, 赤芍) and *Paeoniae radix alba* (baishao, 白芍)	 Paeoniflorin, CAS: 23180-57-6	activate the ERK/CREB pathway and antagonize calcium channel	[97-101]
12	Asiaticoside	*Umbelliferae*	*Centellae herba* (jixuecao, 积雪草)	 Asiaticoside, CAS: 16830-15-2	regulate the PKA/pCREB/BDNF signaling pathway	[104-106]
13	Harmine	*Penganum*	*Peganum harmala L* (luotuopeng, 骆驼蓬)	 Harmine, CAS: 442-51-3	restore astrocytes dsfunction and regulate BDNF or inhibit MAO	[107-109]
14	Silymarin	*Compositae*	*Silybi fructus* (shuifeiji, 水飞蓟)	 Silymarin, CAS: 65666-07-1	promote phosphorylation of ERK and CREB, as well as modulate the expression of BDNF and TrkB	[110-112]
15	Baicalin	*Labiatae*	*Scutellariae radix* (huangqin, 黄芩)	 Baicalin, CAS: 21967-41-9	regulate the NMDAR/NR2B-ERK1/2-related pathway increase the expression of BDNF in the hippocampus by GR/SGK-1/BDNF pathway	[114-116]
16	Paeonol	*Ranunculaceae*	*Moutan cortex* (mudanpi, 牡丹皮)	 Paeonol, CAS: 552-41-0	restore synaptic plasticity through the BDNF-Rac1/RhoA pathway	[117,118]
17	Sinomenine	*Tetrandridae*	*Sinomenii caulis* (qingfengteng, 青风藤)	 Sinomenine, CAS: 115-53-7	prevent NF-κB pathway and NLRP3 inflammasome activation	[123-125]

18	Berberine	*Ranunculaceae*	*Coptidis rhizoma* (huanglian, 黄连)	 Berberine, CAS: 2086-83-1	decline the expression of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α), and inhibit microglial activation and NF-κB signaling pathway	[127,128]
19	Dihydro-myricetin	*Rhamnaceae*	*Semen hoveniae* (zhijuzi, 枳椇子)	 Dihydromyricetin, CAS: 27200-12-0	activate the ERK1/2-CREB pathway and increase phosphorylation of GSK-3β reduce the expression of P2X7R	[129,130]
20	Icariin	*Berberidaceae*	*Epimedii folium* (yinyang-huo, 淫羊藿)	 Icariin, CAS: 489-32-7	inhibit microglial activation and regulate the NLRP3-inflammasome/caspase-1/IL-1β axis regulate the expression of mGluR1, mGluR5, and EAAT2	[132-134]
21	Apigenin	*Umbelliferae*	*Apii herba* (hanqin, 黄芩)	 Apigenin, CAS: 520-36-5	up-regulate the expression of PPARγ to reduce NLRP3 inflammasome	[135-137]
22	Fisetin	*Lacqueraceae*	*Toxicodendri resina* (ganqi, 干漆)	 Fisetin, CAS: 528-48-3	reduce the expression of pro-inflammatory cytokines and iNOS mRNA by modulating the NF-κB pathway	[139,140]
23	Resveratrol	*Grapevine*	*Veratrum nigrum* (huzhang, 虎杖)	 Resveratrol, CAS: 501-36-0	decrease pro-inflammation cytokines and modulate the balance of MDA with GSH	[141-144]

24	Esculetin	*Oleaceae*	*Fraxini cortex* (qinpi, 秦皮)	 Esculetin, CAS: 305-01-1	reduce pro-inflammation cytokines and inflammation-related proteins	[145,146]
25	Crocin	*Iridaceae*	*Croci stigma* (xihonghua, 西红花)	 Crocin, CAS: 42553-65-1	inhibit the NLRP3 inflammasome and NF-κB pathway and suppress microglial activation.	[147,148]
26	Proanthocyanidin	*Elaeagnaceae*	*Hippophae fructus* (shaji, 沙棘)	 Proanthocyanidin, CAS: 18206-61-6	modulate the NF-κB pathway	[149,150]

Conclusion

This paper reviewed the antidepressant activity and effect of various natural products. We classified natural products according to the botanical source and summarized their mechanism of action. Natural products are promising in that they have the great potentiality to treat depressive disorder. However, further animal studies and clinical trials are required to confirm the potential of these compounds as therapeutics for depressive disorder.

Acknowledgement

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Conflicts of Interest

The authors declare no conflict of interest.

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