Extracellular Vesicles: Emerging Roles in Developing Therapeutic Approach and Delivery Tool of Chinese Herbal Medicine for the Treatment of Depressive Disorder

Qian Wu1,2, Wen-Zhen Duan2,3,4, Jian-Bei Chen1, Xiao-Peng Zhao1, Xiao-Juan Li5, Yue-Yun Liu1, Qing-Yu Ma5*, Zhe Xue1* and Jia-Xu Chen1,5*

1School of Traditional Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China, 2Division of Neurobiology, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, United States, 3The Solomon H Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD, United States, 4Program in Cellular and Molecular Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, United States, 5Guangzhou Key Laboratory of Formula-Pattern of Traditional Chinese Medicine, School of Traditional Chinese Medicine, Jinan University, Guangzhou, China

Extracellular vesicles (EVs) are lipid bilayer-delimited particles released by cells, which play an essential role in intercellular communication by delivering cellular components including DNA, RNA, lipids, metabolites, cytoplasm, and cell surface proteins into recipient cells. EVs play a vital role in the pathogenesis of depression by transporting miRNA and effector molecules such as BDNF, IL34. Considering that some herbal therapies exhibit antidepressant effects, EVs might be a practical delivery approach for herbal medicine. Since EVs can cross the blood-brain barrier (BBB), one of the advantages of EV-mediated herbal drug delivery for treating depression with Chinese herbal medicine (CHM) is that EVs can transfer herbal medicine into the brain cells. This review focuses on discussing the roles of EVs in the pathophysiology of depression and outlines the emerging application of EVs in delivering CHM for the treatment of depression.

Keywords: phytochemials, herbal therapies, extracellular vehicles, exosomes, ectosomes, microvesicles, depressive disorder

1 INTRODUCTION

1.1 The Potential Application of Extracellular Vesicles for Promoting Herbal Medicine in Treating Depressive Disorder

Characterized by severe and persistent emotional symptoms, cognitive symptoms, and somatic symptoms (Bhatt et al., 2020), depression is negatively impacting more than 264 million people as one of the most prevalent psychiatric disorders (James et al., 2018). The coronavirus disease 2019 (COVID-19) pandemic has also exacerbated the prevalence of depression (Salari et al., 2020). “Depression” can refer to any of several depressive disorders (DD). Thus, we comprehensively included depression-related works of literature by searching Mesh term “depressive disorder” and all entry terms in PubMed. DD requires long-term treatment, placing a heavy burden on public healthcare systems worldwide. While western medicines, such as tricyclic antidepressants (TCAs), are often prescribed for DD, efficacy can vary among individuals, in addition to detrimental impact...
due to their anticholinergic properties (McClintock et al., 2010) (Prado et al., 2018). Thus, complementary and alternative therapies with fewer adverse effects in treating DD are urgently needed. Traditional Chinese medicine (TCM) treatment includes Chinese herbal medicine (CHM), acupuncture, moxibustion, and naprapathy. The complementary and alternative approach to treating depression is widely applied in China with fewer severe side effects. Many preclinical and clinical studies have demonstrated the antidepressant effects of different Chinese herbal medicine (Wang et al., 2017; Milajerdi et al., 2018; Ruan et al., 2019; Ghasemzadeh Rahbardar and Hosseinzadeh 2020). This paper mainly discusses the potential of herbal therapeutics in TCM for treating DD.

Extracellular vesicles (EVs) are lipid bilayer membrane structures that can carry various nucleic acids, lipids, proteins, and other small metabolites. All cells, including both prokaryotes and eukaryotes, can release EVs as intercellular communication molecules. EVs play vital roles in interrelated physiological and pathophysiological processes, including intercellular communication in the brain. The classification of different EV types is continuously evolving with advances in relevant research (Théry et al., 2018). For example, a study by E. Cocucci suggested that EVs should be broadly categorized as ectosomes or exosomes based on their size and mechanism of formation (Théry et al., 2018) (see Figure 1). Ectosomes are vesicles shed from the superficies of the plasma membrane by budding outside. These structures can vary in diameter from ~50 to 1,000 nm and thus include microparticles, microvesicles and large vesicles (Zhang H. et al., 2018). Exosomes originate from endosomes recycled by exocytosis or endocytosis and range from ~40 to 160 nm in diameter. The formation of exosomes goes through four stages. Firstly, the cup-shaped early-sorting endosome (ESE) consists of soluble proteins related to the extracellular environment and cell surface proteins are formed by endocytosis. Secondly, late-sorting endosomes (LSEs) are matured from ESE. Thirdly, intracellular multivesicular bodies (MVBs) are formed by inward invagination of ESE’s membrane. Finally, MVBs are released by ectocytosis eventually generate exosomes (Kalluri and LeBleu 2020). One hypothesis about the function of EVs proposes that exosomes may take off excessive components in cells to preserve cellular homeostasis (Kalluri and LeBleu 2020). Although the physiological purpose of exosome production remains largely unknown, the studies reviewed in this article indicate that the function, targeting, and particular constituent in exosomes suggest that they could play a significant part by adjusting cell-to-cell communication.

In this article, we deliberate about the application potential of EVs in herbal therapies for DD by summarizing the body of work available in PubMed published over the last 10 years. Hence, this review provides a reference for further research of EVs, particularly in developing CHM for treating DD.

2 THE PATHOGENIC ROLE OF EXTRACELLULAR VESICLES IN DEPRESSION

Depending on the cellular sources, different subcellular components containing DNA, RNA, proteins, lipids, metabolites et al. are delivered into recipient cells by EVs, which can effectively alter the biological response to diseases. The pathogenesis of depression mainly involves synaptic plasticity, oxidative stress, intestinal flora, dysregulation of the hypothalamic pituitary adrenal (HPA) axis, and altered neurotransmitter metabolism and neuroinflammation (Bhatt et al., 2021; Zhang et al., 2021). Signal transmission from one nerve cell to another is essential for synaptic plasticity (Chivet
et al., 2012). Given their prominent role in regulating intercellular communication, more and more researches have explored the potential parts of circulating EVs in the etiopathogenesis of depression via the regulation of neurotransmitters. It has been reported that exosomes are associated with cell-to-cell communication, neuroinflammation, neurogenesis and synaptic plasticity in the brain (Saeedi et al., 2019). These pathophysiological changes in the central nervous system (CNS) reflect EVs’ functional potential and emerging significance in developing DD (see Figure 2). In particular, most preclinical studies have focused on the roles of microRNA (miRNA, see Table 1) or protein (Table 2) contents of EVs in DD.

![FIGURE 2] EVs associated pathogenic changes in DD. EV associated microRNAs and proteins can regulate neurogenesis, neuroinflammation, and synaptic plasticity in the development of DD.

### 2.1 Extracellular Vesicle-Associated microRNAs in Depressive Disorders

MiRNAs are small noncoding RNAs (~22 nucleotides) that perform as post-transcriptional gene regulators through uniting with target messenger RNAs, typically leading to their degradation and subsequent silencing of the target gene (Ramshani et al., 2019). Small (~30–150 nm), secreted EVs transport miRNAs between cells (Valadi et al., 2007; Mathivanan et al., 2010; Théry et al., 2018), enabling these miRNA cargoes to target genes that directly or indirectly contribute to pathological processes (such as accelerating neuroplasticity and brain development) related to depression. For example, one study showed that exosomes isolated from DD patients could cause depressive-like behaviors in normal mice, while exosomes isolated from healthy volunteers and exosomal miR-139-5p apparently alleviated these behavioral changes (Wei ZX. et al., 2020). In addition, exosomal miR-207 was found to alleviate depressive symptoms of stressed mice through targeting Tril, resulting in inhibition of NF-κB signaling in astrocytes (Li et al., 2020). These findings thus supported a relationship between miRNA-bearing exosomes and depression-like behaviors (Li et al., 2020). Collectively, these findings suggest that miRNA-bearing exosomes can attenuate or exacerbate the pathogenesis of depression, although clinical studies are needed to explore these possibilities in humans (see Table 1).

#### TABLE 1 | EV-associated miRNAs and their expression in DD.

| miRNA       | Sample source | Application model/disease | Applied species | Expression | References                      |
|-------------|---------------|---------------------------|-----------------|------------|---------------------------------|
| miR-139-5p  | Blood         | MDD                       | human           | ↑          | (Wei et al., 2020b; Liang et al., 2020) |
| miR-207     | NK cells      | CMS                       | mice            | ↑          | Li et al. (2020)                |
| miR-17-5p   | Blood         | Subthreshold depression    | human           | ↑          | Mizohata et al. (2021)          |
| miR-29c     | Whole-brain lysates and hippocampal | Flinders Sensitive Line depression model  | rats           | ↑          | Choi et al. (2017)              |
| miR-149     | Whole-brain lysates | Flinders Sensitive Line depression model  | rats           | ↑          | Choi et al. (2017)              |

#### TABLE 2 | EV-associated proteins and their potential targets in DD.

| Proteins   | Molecular weight | Model/disease/intervention | Species | Sample source | Expression | References                   |
|------------|------------------|-----------------------------|---------|---------------|------------|------------------------------|
| Aldolase C | ~39 kDa          | Restraint                   | rat     | serum         | ↑          | Gómez-Molina et al. (2019)   |
| Aldolase C | ~39 kDa          | Immobilization              | rat     | serum         | ↑          | Gómez-Molina et al. (2019)   |
| astrocytic GFAP | ~51 kDa         | Restraint                   | rat     | serum         | ↑          | Gómez-Molina et al. (2019)   |
| astrocytic GFAP | ~51 kDa        | Immobilization              | rat     | serum         | ↑          | Gómez-Molina et al. (2019)   |
| synaptophysin | 38 kDa          | Restraint                   | rat     | serum         | ↑          | Gómez-Molina et al. (2019)   |
| synaptophysin | 38 kDa          | Immobilization              | rat     | serum         | ↑          | Gómez-Molina et al. (2019)   |
| reelin     | ~388 kDa         | Restraint                   | rat     | serum         | ↑          | Gómez-Molina et al. (2019)   |
| reelin     | ~388 kDa         | Immobilization              | rat     | serum         | ↑          | Gómez-Molina et al. (2019)   |
| BDNF       | ~13 kDa          | Ketamine                    | rat     | astrocytes    | ↓          | Stemovec et al. (2016)       |
| ILS4       | ~39 kDa          | MDD                         | human   | blood         | ↑          | Kusano et al. (2018)         |
| L1CAM      | 200–220 kDa      | MDD                         | human   | plasma        | ↑          | Nascia et al. (2020)         |
| IRS-1      | 180 kDa          | MDD                         | human   | plasma        | ↑          | Nascia et al. (2020)         |
| Slg-1R     | 25 kDa           | MDD                         | human   | plasma        | ↑          | Wang et al. (2021b)          |
| CD40 ligand| 33 kDa           | MDD                         | human   | plasma        | ↑          | Wallensten et al. (2021)     |
2.2 Extracellular Vesicle-Associated Proteins in Depressive Disorders

Clinical and preclinical proteomics studies have indicated that proteins carried by EVs could potentially serve as biomarkers for depression (Kuwano et al., 2018; Gómez-Molina et al., 2019; Nasca et al., 2020). A study by comparing the proteins in small EVs in two animal models of stress response with depressive-like behaviors has revealed aldolase C, astrocytic GFAP (glial fibrillary acidic protein), synaptophysin (SYP, a synaptic protein), and reelin among the different treatment groups significantly changed (Gómez-Molina et al., 2019; Li et al., 2020). In addition, a study established that SYP, tumor necrosis factor receptor 1 (TNFR1), and interleukin 34 (IL-34) in DD patients’ neuron derived exosomes (NDE) were all positively correlated with the exosomes surface marker cluster of differentiation 81 (CD81) (Kuwano et al., 2018). Another clinical study reported more insulin receptor substrate 1 (IRS-1) in L1 Cell Adhesion Molecule + (L1CAM) exosomes from DD patients. The increased IRS levels in the L1CAM + exosomes were associated with suicidality and anhedonia (Nasca et al., 2020).

In addition to screening for EV-associated protein biomarkers of DD, other studies have explored mechanistic connections between MDD and EV protein cargoes. One such study reported that ketamine could suppress the secretion of BDNF and ATP-triggered EV fusion through decreasing astrocytic Ca^{2+} excitability and elevating the possibility of opening narrow fusion pore (Stenovec et al., 2016). Furthermore, Stenovec et al. found that ketamine can diminish the cytoplasmic mobility of EVs to alter the astroglial ability to regulate extracellular K+ (Stenovec et al., 2020). These cumulative findings suggest that protein-bearing EVs contribute to the development of DD (possibly related to the EV fusion process) and could be potential clinical biomarkers for DD (see Table 2).

3 HERBAL THERAPIES FOR DEPRESSIVE DISORDERS

Herbal therapies are an integral component of traditional Chinese medicines (TCM). Currently, herbal therapies are widely used in China as essential alternative medicine and have been reported to ameliorate clinical symptoms of COVID-19 (Hu et al., 2021). Herbal remedies can be taken in many forms in TCM, and studies into their mechanisms of action and therapeutic efficacy are typically categorized by whether they are administered as herbal formulas (multiple herbs prescriptions), individual herbs, or specific phytochemicals (bioactive herbal constituents) (Hirshler and Doron 2017; Lin et al., 2019).

Below, we discuss the antidepressant effects of these three types of herbal therapies.

3.1 Herbal Formulas for Treating Depressive Disorders

Numerous preclinical and clinical studies of herbal formulas have described the antidepressant effects of herbs such as Yueju (Ren and Chen 2017), Chai Hu Shu Gan San (Sun et al., 2018), or lily bulb and Rehmannia Decoction (Chi et al., 2019). The antidepressant mechanisms differ among these herbal formulas. For example, Bangpungtongsung-San was shown to reduce levels of nitric oxide (NO), inducible nitric oxide synthase (iNOS), cyclooxygenase (COX)-2, tumor necrosis factor-a (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) in a dose-dependent manner via decreased expression of nuclear factor (NF)-κB p65, which suggested that its antidepressant effects were likely related to the suppression of neuroinflammation (Park et al., 2020). By contrast, the antidepressant mechanisms of Jiaweiisinisan appeared to be associated with regulating immune-mediated inflammation, cell apoptosis and synaptic transmission (Chen et al., 2020). In addition, Xiaoyaosan exhibited synergistic antidepressant effects by adjusting Caspase-3 and Nitric oxide synthase-3 (Liu et al., 2021). These studies provide mechanistic evidence that at least partially explains the therapeutic effects of these herbal formulas, although further analytical chemistry is needed to narrow down the contributions of each herbal component.

3.2 Individual Herbs for Treating Depressive Disorders

While herbal formulas comprised of multiple herbal components are commonly prescribed for DD, several herbal therapies reported to provide antidepressant effects use individual herbs, such as Cistanche (Wang et al., 2017), rosemary (Ghasemzadeh Rahbardar and Hosseinzadeh 2020), Angelicae Sinensis Radix (Gong et al., 2019). Senegenin (Li H. et al., 2017), Panax ginseng (Wang W. et al., 2018), Lonicera japonica Thunb (Liu et al., 2019), Polygonum aviculare L. (Park et al., 2018), Hemerocallis citrina (Li CF. et al., 2017), Ginkgo (Zhao et al., 2015) and Armillaria mellea (Vahl) P. Kumm. (Lin et al., 2021). exert the antidepressant effect through inhibiting neuroinflammation. Lycium barbarum deploys a protective effect on depression by promoting neurogenesis (Po et al., 2017). Baicalin exerts an antidepressant effect through enhancing neuronal differentiation (Zhang R. et al., 2019). Perilla frutescens (Ji et al., 2014a), Tribulus terrestris (Wang Z. et al., 2013), and Rehmannia glutinosa Libosch (Wang JM. et al., 2018) alleviate depression by regulating neuroendocrine. Angelicae Sinensis Radix manifests an antidepressant effect by modulating the hematological anomalies (Gong et al., 2019). Agarwood exhibits the antidepressive effect by suppressing the HPA axis (Wang S. et al., 2018). Here we listed herbs that were reported to be effective in treating depression published in the past 10 years (see Table 3).

3.3 Phytochemicals for Treating Depressive Disorders

Although many herbs can exhibit various biological responses, the specific molecular mechanisms of these activities are still mainly uncharacterized. Because of the complexity of multiple chemicals and their efficacies, few herbal pharmacokinetic parameters have been applied successfully for therapeutic monitoring. From the herbal formulas to the individual
phytochemicals, the object of study becomes more precise. Because the structure of phytochemicals is explicit, it is gained more and more attention recently. As chemical compounds produced by herbs, phytochemicals can be used as the basic unit of herbal research. Table 4 presents antidepressant mechanisms of reported phytochemicals in recently 10 years (see Table 4).

### 4 EXTRACELLULAR VESICLES AND HERBAL THERAPIES

Herbal formulas are composed of various herbs, and the individual herb is composed of a variety of phytochemicals. Due to the complex composition of herbal formulas and individual herbs, it is challenging to use EVs to deliver herbal formulas. There are studies using EVs to deliver phytochemicals. A study reported that EVs packaged with curcumin preserve mice from septic shock provoked by lipopolysaccharide (LPS), and it also shown EVs can increase their bioavailability stability and solubility when served as vehicles of curcumin (Sun et al., 2010). Another study reported daily intranasal delivery of curcumin-loaded EVs diminished experimental autoimmune encephalomyelitis, whose mechanism may resulted from increasing induction of apoptosis in microglial cells (Zhuang et al., 2011). These studies demonstrate the potential of EVs for delivering phytochemicals.

In addition, the EVs secreted from cells treated with herb and herb-derived EVs exhibit a therapeutic effect. Ruan et al. found Suxiao Jiuxin pill promotes cardiac mesenchymal stem cells (CMSC) secret exosome through a GTPase-dependent pathway (Ruan et al., 2018a). Exosomes extracted from Suxiao Jiuxin pill-treated CMSC can also decline the expression of H3K27 demethylase UTX, furthermore, enhance cardiomyocyte proliferation (Ruan et al., 2018b). Besides EVs secreted by cells treated with herbal formulas, the EVs isolated from plant samples also had therapeutic functions (Kim et al., 2021). Vesicles derived from plants are structural units composed of various primary and secondary metabolites, which play a synergistic role in biological transport and pharmacodynamics (Cao et al., 2019b). Zhang et al. reported that plant cell secrets, EVs, and plant-derived EVs could be a new therapeutic method against diseases (Zhang et al., 2016c). For example, EVs-liked ginseng-derived nanoparticles (GDNPs) can be recognized and internalized with macrophages and induce M1-type polarization of macrophages to inhibit melanoma growth in mice (Cao et al., 2019c). Exosomes derived from ginseng can promote the neural differentiation of bone marrow derived mesenchymal stem cells (Xu et al., 2021). In addition, the targeting specificity of plant-derived EVs can also be improved by modifying their surface. For example, folate-conjugated arrowtail pRNA-3WJ were reported to facilitate the binding and uptake of ginger-derived exosome-like nanovesicles to NK cells (Li et al., 2018).

Moreover, EVs are used as biomarkers in herbal research. For example, Platelet-derived microvesicles (PMVs) were the indicator of platelets activation in a study that explores Tanshinone IIA’s function in a cluster of differentiation 36 (CD36) and mitogen-activated protein kinase kinase 4/c-Jun NH 2 terminal kinase (MKK4/JNK2) signaling pathway (Wang H. et al., 2020). Tanshinone IIA also elicited its function in a cluster of differentiation 36 by provoking endothelial microparticles production (Liu et al., 2021). These studies demonstrate the potential of EVs for delivering phytochemicals.
| Phytochemicals          | Molecular weight | Original medical herbs       | Model | Species            | Antidepressant mechanism                                                                 | References         |
|------------------------|------------------|------------------------------|-------|--------------------|------------------------------------------------------------------------------------------|--------------------|
| Trans-cinnamaldehyde   | 132.16 g/mol     | Ramulus Cinnamomi            | FST   | mice               | ↓5-HT, Glu/GABA; ↓COX-2, TRPV1, OB1                                                   | Lin et al. (2019)  |
| Trans-cinnamaldehyde   | 132.16 g/mol     | Cinnamomum cassia            | CUMS  | rats               | ↓TLR4, NF-κB, p-p65, TNF-α, NLRP3, ASC, caspase-1, IL-1β, and IL-18 in the prefrontal cortex and hippocampus | Wang et al. (2020b) |
| Perillaldehyde         | 150.22 g/mol     | Perilla frutescens           | LPS   | mice               | ↓the levels of TNF-α and IL-6 in both the serum and the prefrontal cortex; ↑5-HT and NE in the prefrontal cortex | Ji et al. (2014b)  |
| Perillaldehyde         | 150.22 g/mol     | Perilla frutescens           | CUMS  | rats               | ↓TXNIP, NLRP3, Cleaved caspase-1 and p-NF-κB p65 in the hippocampus                   | Song et al. (2018) |
| Ferulic acid           | 194.18 g/mol     | Radix Glycyrrhiza            | CUMS  | mice               | ↓IL-1β, IL-6, TNF-α, NF-κB, NLRP3 in the prefrontal cortex                            | Liu et al. (2017b) |
| Resveratrol            | 228.24 g/mol     | Veratrum album               | Ouabain| mice              | ↓IL-1β, IL-17A, IL-8, TNF-α in plasma                                                  | Wang et al. (2018a) |
| Resveratrol            | 228.24 g/mol     | Veratrum album               | CUMS  | rats               | ↓CORT in plasma and CRH mRNA in the hypothalamus; ↓IL-6, CRP, TNF-α in plasma          | Yang et al. (2017) |
| Honokiol               | 266.3 g/mol      | Magnolia officinalis         | LPS   | mice               | ↓TNF-α, IL-1β, IDO, IFN-γ, free calcium in brain tissue; ↓quinoic acid in brain tissue; ↓mRNA of TNF-α, IL-1β, IL-6, IL-8 | Zhang et al. (2019a) |
| Baicalein              | 270.24 g/mol     | Scutellaria baicalensis      | EAP   | mice               | ↓cAMP, PKA C-α, and p-CREB the proliferation of neurons; ↓SERTs                       | Du et al. (2019)   |
| Helicid                | 284.2 g/mol      | Helicia nilagrica            | CUMS  | rats               | ↑NSCs proliferation in the hippocampus; ↓p-iκB, NF-κB, IL-1β                           | Li et al. (2019)   |
| Gastrodin              | 286.26 g/mol     | gastrodia elata              | CUS   | rats               | ↓NSCs proliferation in the hippocampus; ↓β-actinin, GFAP, IL-1β                          | Wang et al. (2014b) |
| Salidroside            | 300.3 g/mol      | Rhodiola rosea               | Olfactory bulbectomized | mice | ↑GR, BDNF in the hippocampus; ↓CRH in the hypothalamus | Yang et al. (2014) |
| Salidroside            | 300.3 g/mol      | Rhodiola rosea               | Olfactory bulbectomized | mice | ↑ERK1/2, CREB, pAkt, BDNF in the hippocampus, hippocampal neurogenesis | Liu et al. (2017a) |
| Z-guggulsterone        | 312.4 g/mol      | Commiphora mukul             | CUS   | mice               | ↑TNF-α, IL-1β, IFN-γ, free calcium in brain tissue; ↓quinoic acid in brain tissue; ↓mRNA of TNF-α, IL-1β, IL-6, IL-8 | Zhang et al. (2019a) |
| 3-(3,4-methylenedioxy-5-| 315.29 g/mol     | Piper laetispicum            | LH and SDS | mice | ↑TSPO, VADC1, Park, Beclin 1, KIFC2, Snap25                                             | Wei et al. (2020a) |
| trifluoromethyl phenyl)-2E-propanoic acid isobutyl amide | | C, DC | | | |
| Sinomenine             | 329.4 g/mol      | Sinomenium acutum            | CUMS  | mice               | ↑NE and 5-HT in the hippocampus, NLRP3, IL-1β, IL-6, and TNF-α in the hippocampus         | Liu et al. (2018)  |
| Andrographolide        | 350.4 g/mol      | Andrographis paniculata      | CUMS  | mice               | ↑NO, COX-2, INOS, IL-1β, IL-6, TNF-α, p-p65, p-κBα, NLRP3, ASC, caspase-1 in the prefrontal cortex | Geng et al. (2019) |
| Curcumin               | 368.4 g/mol      | Rhizoma Curcumaes longae     | CUMS  | rats               | ↓IL-1β, IL-6, TNF-α and NF-κB                                                          | Fan et al. (2018)  |
| Curcumin               | 368.4 g/mol      | Rhizoma Curcumaes longae     | CUMS  | rats               | ↓mRNA of IL-1β, IL-6, TNF-α, NF-κB                                                      | Zhang et al. (2019c) |
| 2,3,5,4'-Tetrahydroxystilbene-2-O-beta-D-glucoside | 406.4 g/mol | Polygonum multiflorum | CRS  | mice               | ↑TNF-α, IL-1β, IL-6 in hippocampal and prefrontal cortex                              | Jiang et al. (2018) |
| 2,3,5,4'-Tetrahydroxystilbene-3-O-beta-D-glucoside | 406.4 g/mol | Polygonum multiflorum | LPS  | mice               | ↑IL-1β, IL-6, TNF-α, and oxidoredox-stress hippocampus and prefrontal cortex          | Chen et al. (2017) |
| Puerarin               | 416.4 g/mol      | Radix Bupleuri               | CUS   | rats               | ↑progesterone, allopregnanolone, 5-HT, and 5-HIAA in the prefrontal cortex and hippocampus | Qiu et al. (2017)  |
| Baicalin               | 446.4 g/mol      | Scutellaria baicalensis Georgi | CUMS  | mice               | ↑neurogenesis, p-Akt, FOXG1, FG2                                                       | Zhang et al. (2019b) |
| Baicalin               | 446.4 g/mol      | Scutellaria baicalensis Georgi | CUMS  | mice               | ↑IL-1β, IL-6, TNF-α in the hippocampus, and TLR4; ↑pIP3K, AKT, and FoxO1              | Guo et al. (2019)  |
| Baicalin               | 446.4 g/mol      | Scutellaria baicalensis Georgi | CUMS  | mice               | ↑DCX, NSE, BDNF in the hippocampus, SOD; ↑caspase-1, IL-1β in the hippocampus, MDA.   | Zhang et al. (2018b) |
| Baicalin               | 446.4 g/mol      | Scutellaria baicalensis Georgi | Corticosterone | mice | ↑the protein of 11β-HSD2 in the hippocampus, mRNA, and protein of GR        | Li et al. (2015)   |

(Continued on following page)
TABLE 4 | (Continued) Antidepressant mechanism of phytochemicals.

| Phytochemicals | Molecular weight | Original medical herbs | Model | Species | Antidepressant mechanism | References |
|----------------|------------------|------------------------|-------|---------|---------------------------|------------|
| Iridoids       | 456.4 g/mol      | Gardeniae fructus SRS  |       | mice    | and BDNF; ↓SGK1 in the hippocampus and serum | Xia et al. (2021) |
| Paeoniflorin   | 480.5 g/mol      | Radix Paeoniae Alba Interferon-alpha  |       | mice    | ↓GLuA1, p-Akt/Akt, p-mTOR/mTOR, p-p70S6K, PSD-95, Synapsin-1 | Li et al. (2017d) |
| Senegenin      | 537.1 g/mol      | Polygalan tenuifolia Wild |       | mice    | ↓IL-6, IL-10,TNF-α in the medial prefrontal cortex | Li et al. (2017c) |
| Icarin         | 676.7 g/mol      | Epimedium herb Ovary remove and CUS | rats  | ↑AKT, p-AKT, PI3K (110 kDa, 85 kDa), Bcl-2 in the ovaries; ↑Bax | Cao et al. (2019a) |
| Icarin         | 676.7 g/mol      | Herba Epimedi OMS | rats  | ↑TNF-α, IL-1β, NF-κB, NLRP3, mRNA of iNOS, ↓p-IκBα, p65 | Liu et al. (2018) |
| Salvianolic acid B | 718.6 g/mol | Salvia miltiorrhiza Bunge | CMS | rats | ↑NLRP3, MDA; ↑CAT, SOD, GPx | Huang et al. (2019) |
| Salvianolic acid B | 718.6 g/mol | Salvia miltiorrhiza Bunge | CMS | rats | ↓IL-1β, TNF-α, apoptosis, and microglia activation in the hippocampus and cortex; ↓IL-10, TGF-β in the hippocampus and cortex | Zhang et al. (2016a) |
| Saikosaponin A | 781 g/mol        | Bupleurum chinense MCAO with CUMS and isolation | rats  | ↑Bax, Caspase-3, hippocampal neuronal apoptosis; ↑BDNF, p-CREB and Bcl-2 | Wang et al. (2021a) |
| Saikosaponin-D | 781 g/mol        | Bupleurum chinense LPS | mice  | ↑HMGB1 translocation from nuclear to extracellular, TLR4, p-κBα, NF-κBp65 | Su et al. (2020) |
| Saikosaponin-D | 781 g/mol        | Bupleurum chinense CUMS | rats  | ↑DCX, p-CREB, BDNF. | Li et al. (2017b) |
| Ginsenoside Rg3 | 785 g/mol       | Panax ginseng LPS | mice  | ↑mRNA of pro-inflammatory cytokines, IDO; ↓IL-6, TNF-α in plasma | Kang et al. (2017) |
| Ginsenoside Rg3 | 785 g/mol       | Panax ginseng CUMS | rats  | ↑progesterone, allopregnanolone, 5-HT in the prefrontal cortex and hippocampus; ↓CRH, CORT, ACTH, ↓SOD, GSH-Px; ↑MDA, NO, ROS, 4-HNE, 8-OHdG | Xu et al. (2018) |
| Ginsenoside-Rg1 | 801 g/mol       | Panax ginseng CUMS | rats  | ↑CORT in serum; ↑testosterone in serum, GR protein in the PFC and hippocampus | Cao et al. (2019b) |
| Ginsenoside-Rg1 | 801 g/mol       | Panax ginseng CUMS | rats  | ↓INOS, COX2, caspase-9, caspase-3, iNOS1 in the hippocampus, IL-6, TNF-α, ↓β2 | Mou et al. (2017) |
| Ginsenoside-Rg1 | 801 g/mol       | Panax ginseng CSDS | mice  | ↑p-Akt/Akt, p-mTOR/mTOR, p-p70S6K, PSD-95, Synapsin-1, IL-6, TNF-α, IL-1β | Jiang et al. (2020) |
| Chiisanoside   | 955.1 g/mol      | Acanthopanax sessiliflorus | LPS  | mice  | ↓IL-6, TNF-α in serum, BDNF, TrkB, NF-κB in hippocampus; ↑SOD and MDA; ↓CD16/32 (M1), INOS, NF-κB, p65, NLRP3, cleavage caspase-1; ↑CD206 (M2) in the hippocampus | Bian et al. (2018) |
| Crocin         | 977 g/mol        | Gardenia jasminoides and Crocus sativus | LPS  | mice  |                           | Zhang et al. (2018d) |

Bolbostemma paniculatum (Maxim.), efficiently lead to in vitro and in vivo micropinocytosis, which is able to traffic small molecules into colorectal cancer (CRC) cells (Gong et al., 2018). Another study demonstrated that matrine could induce macropinocytosis and the regulation of adenosine triphosphate (ATP) metabolism (Zhang B. et al., 2018). In Fructus Meliae Toosendan -induced liver injury mice, serum exosomal miR-222 and miR-370-3p were reported as significantly downregulated miRNAs (Zheng et al., 2018; Yu et al., 2020). By suppressing TGF1 exosomes transferring from Glomerular mesangial cells to glomerular endothelial cells, Tongxinluo can impede renal fibrosis in diabetic nephropathy (Wu et al., 2017). Buyang Huanwu Decoction can enhance angiogenic by elevating miRNA-126 levels in mesenchymal stem cell secreted exosomes (Yang et al., 2015).

5 FUTURE PERSPECTIVES

5.1 Extracellular Vesicles: A New Delivery Approach for Treatments of Depression?

Blood-brain barrier (BBB) restricts the substances passing between the CNS and the vascular circulation system, thereby protecting the CNS from exposure to overactive immune responses or toxic substances (Obermeier et al., 2013; Andreone et al., 2015). Since the substrates from the blood to the CNS is controlled by the BBB (Kadry et al., 2020), effective drug transfer to the brain poses a challenge for treating CNS disorders, including neurodegenerative diseases, stroke, autoimmune diseases, or neuropsychiatric diseases like DD (Abbott et al., 2006; Upadhayay 2014). Almost all large molecule biologics and about 98% of small molecule...
drugs cannot traverse the BBB (Pardridge 2012). Nevertheless, the BBB permits transmembrane diffusion of lipid soluble (lipophilic) molecules smaller than 400 Da and can selectively transport some compounds into and out of the brain (Sanchez-Covarrubias et al., 2014). In this context, EVs could have advantages as drug vehicles, such as their small size, low immunogenicity, and ability to cross the BBB carrying cellular components or pharmacological agents (see Figure 3). Since EVs have the regenerative ability, they can also be exploited to potentially inhibit ongoing neurodegenerative processes associated with DD (Bhatt et al., 2021). Previous research has established the successful transmission of exosomes to the brain in mice via intranasal injection or intravenous administration (Zhuang et al., 2011; Yuan et al., 2017). Another study also showed that exosomes could pass over the BBB and communicate bi-directionally between the brain and the rest of body (Bhatt et al., 2021). Despite the expected benefits of EVs for the treatment of DD, precise mechanisms of action and routes of delivery still require careful and rigorous investigation (Bhatt et al., 2021).

Herbal compounds are derived from diverse natural products. Since Chinese herbal concoctions are complex and undefined mixtures, it is challenging to demonstrate which component of the herbal therapy is responsible for a given effect (Corson and Crews 2007; Xu 2011). In particular, small phytochemicals could serve as viable cargoes for EV delivery (Liu et al., 2021)( Li et al., 2021). Indeed, studies exploring the application of EVs as vehicles for drug delivery have already begun. For example, curcumin-loaded EVs were found to protect mice from lipopolysaccharide (LPS)- induced septic shock (Sun et al., 2010). However, very few studies have examined DD treatment with phytochemical-loaded EVs, suggesting great potential for this line of research. For further references of phytochemical-loaded EVs research of DD, we screened potential phytochemicals from Table 4 by Lipinski’s rule of five, the rule of thumb to evaluate if a chemical compound has chemical properties and physical properties would make it an orally active drug in humans (see Table 5).

Besides serving as cargoes for EV delivery, herbs can also be applied to be the vehicle of EV. Distinct from artificially fabricated liposomes, plant-derived nanovector was reported to transport chemotherapeutic agents through mammalian hindrances such as BBB, and refrain from inflammatory response or necrosis (Wang Q. et al., 2013). Moreover, the lipid bilayer structure of plant-derived nanovector can protect

![FIGURE 3](image-url) EVs for DD treatment by drug delivery. Phytochemicals such as Trans-cinnamaldehyde (TCA), Baicalein (BAI), Helicid (HEL), Z-guggulsterone (ZGU) and Sinomenine (SIN) can be packaged into extracellular vesicles and conveyed through the BBB to the brain cells (neurons and neuroglial cells), and exert antidepressant effect by regulating neuroinflammation, neurogenesis and neurotransmitter metabolism through a variety of pathways.
the cargo from the enzymatic decomposition of proteases and nucleases (Wang et al., 2015). Since plants do not retain zoonotic or human pathogens, plant-derived EVs take advantage of non-immunogenic and innocuous compared with mammalian cell-derived EVs (Schuh et al., 2019; Dad et al., 2021). On the other side, plant-derived EVs do not have cell targeting specificity because they have no ligands in comparison to mammalian cell-derived EVs. Previous studies reported that plant-derived EVs arrive at the liver and intestines through their natural biodistribution properties (Wang B. et al., 2014; Zhuang et al., 2015; Zhang et al., 2016b). Fortunately, plant-derived EVs can obtain specific cellular targeting by modification (Wang Q. et al., 2013).

### 5.2 Herb-Derived Extracellular Vesicles: Emerging Therapeutics for Depression?

As mentioned before, plant-derived EVs are beneficial to be the vehicle of phytochemicals since they are innocuous, low immunogenicity, and editable for target specificity. They can also promote cellular uptake and have higher stability in the GI tract (GIT) (Fujita et al., 2018), and the versatile therapeutic potential of plant-derived EVs rooted in their active source plants (Mu et al., 2014). Moreover, EVs extracted from the plant have been reported to be introduced via oral (Wang B. et al., 2014; Zhang et al., 2017), intravenous (Li et al., 2018), intramuscular, and intranasal administration (Wang Q. et al., 2013; Ju et al., 2013). This is another advantage of herb-derived EVs compared with Chinese herb decoction because the component complexity is always troubling applying effective Chinese herb to intramuscular, intravenous, and intranasal administration. These characteristics above make herb-derived EVs attractive to be an emerging therapeutic. Although many research have explained the anti-depressant mechanism of Chinese herbs (see Table 3), few studies explored the effect of Chinese herb-derived EVs in treating depression, which is an exciting direction required to be followed.

### 5.3 Extracellular Vesicles: Potential Biomarkers for Diagnostic Depression

The unique property of EVs that can easily traverse BBB makes EVs a potential early diagnostic marker of CNS disorders like depression (Chen et al., 2016; Yao et al., 2018; Cufaro et al., 2019). Candidate protein biomarkers and potential diagnostic miRNAs for DD have been suggested (Al Shweiki et al., 2017; Tavakolizadeh et al., 2018; Saeedi et al., 2019). Besides miRNAs and proteins, exosomes as nanocarriers own the potential to be diagnostic biomarkers in various CNS disorders including DD (Perets et al., 2018; Wallensten et al., 2021).

The reasons why exosomes have the potential to be clinical diagnostics and biomarker are as follow (Kanninen et al., 2016): Firstly, exosomal contents can be changed along with disease conditions, which can reflect the dynamic state of disease in real-time; Secondly, exosomes can be easily extracted non-invasively from biological fluids (Bhatt et al., 2021), which is particular important because non-invasive availability is beneficial to early diagnosis of DD; Thirdly, exosomal contents are protected by the membranous structure, which keeps off the degradation of potential biomarkers (Kanninen et al., 2016); Fourthly, exosomes are very stable and can be preserved for prolonged periods (Grapp et al., 2013), making their clinical application feasible; Fifthly, exosomes can express their original cellular surface markers, so that they can be traced to their origin; Last but not least, since exosomes are able to pass over the BBB, which provide information of CNS cells that is hard to obtain without invasive techniques (Boukouris and Mathivanan 2015; Kawikova and Askenase 2015; Lin et al., 2015; Aryani and Denecke 2016). Because exosomes are distributed in all biological fluids and all cells can secret them, their biogenesis enables the arresting of the complex extracellular and intracellular molecular cargo (Kalluri and LeBlu 2020), rendering exosome-based liquid biopsy attractive in diagnosing the prognosis of DD. Liquid biopsies can allow us to understand the pathophysiology change of DD and diagnose the progressive disorders in the early stages (Topuzoglu and Ilgın 2020). Moreover, studies relating the biomarkers associated with EVs in the context of

| Phytochemicals         | Molecular weight | Hdon | Hacc | AlogP | RBN  | Lipinski’s rule | OB (%) | BBB   |
|------------------------|------------------|------|------|-------|------|-----------------|--------|-------|
| Honokiol               | 266.3 g/mol      | 2    | 2    | 4.83  | 5    | Yes             | 60.67  | 0.92  |
| Z-guggulsterone        | 312.4 g/mol      | 0    | 2    | 3.75  | 0    | Yes             | 42.45  | 0.33  |
| Ferulic acid           | 194.18 g/mol     | 2    | 3    | 2.36  | 3    | Yes             | 40.43  | 0.56  |
| Perillaldehyde         | 150.22 g/mol     | 0    | 1    | 2.67  | 2    | Yes             | 39.00  | 1.57  |
| Baicalein              | 270.24 g/mol     | 3    | 5    | 2.35  | 1    | Yes             | 33.52  | -0.05 |
| Trans-cinnamaldehyde   | 132.16 g/mol     | 0    | 1    | 1.96  | 2    | Yes             | 31.99  | 1.48  |
| Sinomenine             | 329.4 g/mol      | 1    | 5    | 1.32  | 2    | Yes             | 30.98  | 0.43  |
| Resveratrol            | 228.24 g/mol     | 3    | 3    | 3.01  | 2    | Yes             | 19.07  | -0.01 |
| Gastrodin              | 286.28 g/mol     | 5    | 7    | -0.95 | 4    | Yes             | 8.19   | -2.29 |
| Salidroside            | 300.3 g/mol      | 5    | 7    | -0.47 | 5    | Yes             | 7.01   | -1.41 |
| Curcumin               | 368.4 g/mol      | 3    | 6    | 3.36  | 7    | Yes             | 5.15   | -0.76 |

Hdon and Hacc are possible number hydrogen-bond donors and acceptors, respectively; RBN, means the number of the bonds allowing free rotation around themselves; AlogP value is the partition coefficient between octanol and water, which is crucial for measuring hydrophobicity of molecule; OB: oral bioavailability; BBB: blood-brain barrier; BBB < -0.3 were considered as non-penetrating (BBB-), from -0.3 to +0.3 moderate penetrating (BBB±), and >0.3 strong penetrating (BBB+).
DD still need more exploration. However, with the utility of liquid biopsy in diagnosing the prognosis of DD, the multicomponent analysis of EVs in the future may determine the disease progression and response to treatment.

5.4 Extracellular Vesicles: A Connection Bridge Between Herbal Therapies for Depression and Metabolomics, Proteomics, Transcriptomics and Epigenetics Studies

Metabolomics is a discipline to obtain all information of metabolites in a biological sample and would give mechanistic insights into the etiology of DD (Nedic Erjavec et al., 2018; Du et al., 2022). For example, nine potential biomarkers involved the depression pathogenesis were identified based on metabolomics analysis by comparing the rats’ serum metabolites of CUMS(chronic unpredictable mild stress) model group and Xiao-Chai-Hu-Tang group (Xiong et al., 2016). Proteomics includes all levels of protein composition, structure, and activity exploration of proteomes. Shweiki et al. summarized 42 differentially regulated proteins in DD and discussed the diagnostic potential of the biomarker candidates and their association with the suggested pathologies (Al Shweiki et al., 2017). Transcriptomics is the study associated with the process of all RNA transcripts during the biological process of transcription, and many transcriptomics studies provide insight into DD (Belzeaux et al., 2018; Cho et al., 2019; Rainville et al., 2021). By transferring key miRNAs, exosomes from the neuron, astrocyte, and neural progenitor cell exhibited significant efficiency in promoting neurogenesis (Takeda and Xu 2015; You et al., 2020; Yuan et al., 2021). Xu et al. systematically identified the miRNAs of exosomes from the juice of ginseng by transcriptomic technology, and found 44 kinds of miRNAs perfectly match to the ginseng genome database (Xu et al., 2021).

Epigenetics covers heritable phenotype changes that are not involved in alterations of the DNA sequence, which is associated with DD reported by numerous studies (Yeshurun and Hannan 2019; Wheater et al., 2020; Xu et al., 2020). As discussed above, EVs are ideal herbal drug carriers due to their remarkable biocompatibility. Moreover, since DNA, RNA, lipids, proteins, cytoplasm, and metabolites are delivered by EVs, it can be taken as the critical point connecting herbal therapies to metabolomics, proteomics, transcriptomics and epigenetics in DD (see Figure 4).

6 CONCLUSION

Although CHM has been applied in China for thousands of years to help people fight many diseases, and some of Chines herbal original phytochemicals such as artemisinin have already been proved effective, composition complexity still remains a strenuous challenge for the mechanistic studies of CHM. Opportunely, the cargos and ligands of EVs can be determined by metabolomics, proteomics, and transcriptomics technologies, which means that the composition of herb-derived EVs can be specified for further mechanism study. Once the composition is precise, it can also be applied to different delivery routes such as intravenous or intranasal administration, which used to be limited to explore by the composition complexity of CHM. In addition, non-immunogenic, innocuous, and target-specific features make herb-derived EVs attractive to be therapeutic agents.

EVs can serve as drug vehicles for phytochemicals and biomarkers in developing the treatment for DD. Trials in intranasal administration of EVs indicate their significance in CNS diseases and show high promise to be a new medical way to transfer phytochemicals across the BBB. Since there are no
specific biomarkers available for DD, the diagnosis has to depend on the combination of psychiatric evaluation, physical exam and lab tests. However, combined with metabolomics, proteomics, transcriptomics, and epigenetics technologies, the specifically altered contents in EVs from DD patients can be measured.

Even though EVs own promising advantages for delivering CHM, especially effective phytochemicals for treating DD, the components complexity of herbs and herbal formulas makes it challenging to be delivered by EVs. Moreover, there are few studies on pharmacological functions and in vivo transport pathways of CHM-derived EVs, which need more exploration before clinical practice. Therefore, the CHM study of EVs is still in the initial stage. More in-depth study in different CHM-derived EVs will be helpful to explain the complicated pharmacology of CHM and develop a new administration mode.

This review has summarized the reported effective CHM for treating DD and the advantages of EVs in facilitating CHM for DD treatment. Currently, few studies have been focused on herb-derived EVs in treating DD, which is exciting but remains to be explored in this area.

REFERENCES

Abbott, N. J., Rönnbäck, L., and Hansson, E. (2006). Astrocyte-endothelial Interactions at the Blood-Brain Barrier. Nat. Rev. Neurosci. 7, 41–53. doi:10.1038/nrn1824

Al Shweiki, M. R., Oeckl, P., Steinacker, P., Hengerer, B., Schönfeldt-Lecuona, C., and Otto, M. (2017). Major Depressive Disorder: Insight into Candidate Cerebrospinal Fluid Protein Biomarkers from Proteomics Studies. Expert Rev. Proteomics 14, 499–514. doi:10.1080/14789495.2017.1336435

Andreonie, B. J., Lacoste, B., and Gu, C. (2015). Neuronal and Vascular Interactions. Annu. Rev. Neurosci. 38, 25–46. doi:10.1146/annurev-neuro-071714-033835

Aryani, A., and Denecke, B. (2016). Exosomes as a Nanodelivery System: a Key to the Future of Neuromedicine? Mol. Neurobiol. 53, 818–834. doi:10.1007/s12035-014-9054-5

Belzeaux, R., Lin, R., Ju, C., Chay, M. A., Fiori, L. M., Lutz, P. E., et al. (2018). Transcriptomic and Epigenomic Biomarkers of Antidepressant Response. J. Affect. Disord. 233, 36–44. doi:10.1016/j.jad.2017.08.087

Bhatt, S., Kanoujia, J., Drar, A. K., Arumugam, S., Silva, A. K. A., and Mishra, N. (2021). Exosomes A Novel Therapeutic Paradigm for the Treatment of Depression. Curr. Drug Targets 22, 183–191. doi:10.2174/1389450121999000106193005

Bhatt, S., Nagappa, A. N., and Patil, C. R. (2020). Role of Oxidative Stress in Depression. Drug Discov. Today 25, 1270–1276. doi:10.1016/j.drudis.2020.05.001

Bian, X., Liu, X., Liu, J., Zhao, Y., Li, H., Cai, E., et al. (2018). Study on Antidepressant Activity of Chiasmanoiside in Mice. Int. Immunopharmacol. 57, 33–42. doi:10.1016/j.intimp.2018.02.007

Boukouris, S., and Mathivanan, S. (2015). Exosomes in Bodily Fluids Are a Highly Stable Resource of Disease Biomarkers. Proteomics Clin. Appl. 9, 358–367. doi:10.1002/prca.201400114

Cao, L. H., Qiao, J. Y., Huang, H. Y., Fang, X. Y., Zhang, R., Miao, M. S., et al. (2019a). PI3K-AKT Signaling Activation and Icaritin: The Potential Effects on the Perimenopausal Depression-like Rat Model. Molecules 24. doi:10.3390/molecules2403700

Cao, M., Yan, H., Han, X., Weng, L., Wei, Q., Sun, X., et al. (2019c). Ginseng-Derived Nanoparticles Alter Macrophage Polarization to Inhibit Melanoma Growth. J. Immunother. Cancer 7, 326. doi:10.1186/s40425-019-0817-4

Cao, M., Yan, H. H., Han, X., Weng, L., Wei, Q., Sun, X., et al. (2019b). Astrocytes at the Hub of the Stress Response: Potential Modulation of Neurogenesis by miRNAs in Astrocyte-Derived Exosomes. J. Ethnopharmacol. 177, 144–158. 10.1016/j.jep.2020.05.017. doi:10.1016/j.jep.2020.05.017

Chen, C. C., Liu, L. M., Ma, F., Wong, C. W., Guo, X. E., Chacko, J. V., et al. (2016). Elucidation of Exosome Migration across the Blood-Brain Barrier Model In Vitro. Cell. Mol. Bioeng. 9, 509–529. doi:10.1007/s12195-016-0458-3

Chen, J., Huang, Y., Li, L., Niu, J., Ye, W., Wang, Y., et al. (2020). Antidepressant Pathways of the Chinese Herb Jiaweisinansan through Genetic Ontology Analysis. J. Integr. Neurosci. 19, 385–395. doi:10.1108/jin.2020.02.1246

Chen, Z., Huang, C., He, H., and Ding, W. (2017). 2, 3, 5, 4′-Tetrahydroxystilbene-2-O-β-D-Glucoside Prevention of Lipopolysaccharide-Induced Depressive-like Behaviors in Mice Involves Neuroinflammation and Oxido-Nitrosative Stress Inhibition. Behav. Pharmacol. 28, 356–374. doi:10.1097/FBP.0000000000000307

Chi, X., Wang, S., Baloch, Z., Zhang, H., Li, X., Zhang, Z., et al. (2019). Research Progress on Classical Traditional Chinese Medicine Formula Lilly Bulb and Rehmannia Decocton in the Treatment of Depression. Biomed. Pharmacother. 112, 108616. doi:10.1016/j.biopha.2019.108616

Chivet, M., Hemming, F., Pernet-Gallay, K., Fraboulet, S., and Sadoul, R. (2012). Emerging Role of Neuronal Exosomes in the central Nervous System. Front. Physiol. 3. 145. doi:10.3389/fphys.2012.00145

Cho, J. H., Irwin, M. R., Eisenberger, N. I., Lamkin, D. M., and Cole, S. W. (2019). Transcriptomic Predictors of Inflammation-Induced Depressed Mood. Neuropsychopharmacology 44, 923–929. doi:10.1038/s41386-019-0316-9

Choi, J. L., Kao, P. F., Iriago, E., Zhan, Y., Kozubek, J. A., Hoss, A. G., et al. (2017). miR-149 and miR-29c as Candidates for Bipolar Disorder Biomarkers. Am. J. Med. Genet. B Neuropsychiatr. Genet. 174, 313–323. doi:10.1002/ajmg.b.32518

Corson, T. W., and Crews, C. M. (2007). Molecular Understanding and Modern Application of Traditional Medicines: Triumphs and Trials. Cell 130, 769–774. doi:10.1016/j.cell.2007.08.021

Cufaro, M. C., Piergostino, D., Lanuti, P., Rossi, C., Cicalini, L., Federici, L., et al. (2019). Extracellular Vesicles and Their Potential Use in Monitoring Cancer Progression and Therapy: The Contribution of Proteomics. J. Oncol. 2019, 1639854. doi:10.1155/2019/1639854

Dad, H. A., Gu, T. W., Zhu, A. Q., Huang, L. Q., and Peng, L. H. (2021). Plant Exosome-like Nanovesicles: Emerging Therapeutics and Drug Delivery Nanoplatforms. Mol. Ther. 29, 13–31. doi:10.1016/j.ymthe.2020.11.030

Du, H. X., Chen, X. G., Zhang, L., Liu, Y., Zhan, C. S., Chen, J., et al. (2019). Microglial Activation and Neurobiological Alterations in Experimental Autoimmune Prostateitis-Induced Depressive-like Behavior in Mice. Neuropsychiatr. Dis. Treat. 15, 2231–2245. doi:10.2147/NPD.T211288

Du, Y., Dong, J. H., Chen, L., Liu, H., Zheng, G. E., Chen, G. Y., et al. (2022). Metalloprotein Identification of Serum Exosome-Derived Biomarkers for Bipolar Disorder. Oxid. Med. Cell. Longev. 2022, 5717445. doi:10.1155/2022/5717445

AUTHOR CONTRIBUTIONS

QW completed the literature review and wrote the review, W-ZD thoroughly reviewed and edited the review, J-BC extracted helpful information from included studies, X-PZ helped with the abstract, X-JL classified the pieces of literature, Y-YL helped check the writing of the essay, ZX helped with the tables and the revision of the whole manuscript, Q-YM and J-XC, as primary reviewers screened titles and abstract for eligibility. All authors read and approved the final manuscript.

FUNDING

This research work and publication were financially supported by Key Program of National Natural Science Foundation of China (No. 81630104), National Natural Science Foundation of China (No. 81973748, No. 82174278), Youth Science Fundation Project of National Natural Science Foundation of China (No. 81803972).
Obermeier, B., Daneman, R., and Ransohoff, R. M. (2013). Development, Maintenance and Disruption of the Blood-Brain Barrier. Nat. Med. 19, 1584–1596. doi:10.1038/nm.3407

Partridge, W. M. (2012). Drug Transport across the Blood-Brain Barrier. J. Cereb. Blood Flow Metab. 32, 1959–1972. doi:10.1038/jcbfm.2012.126

Park, B. K., Kim, N. S., Kim, Y. R., Yang, C., Jung, I. C., Jang, I. S., et al. (2020). Antidepressant and Anti-neuroinflammatory Effects of Bangungtongsung-San. Front. Pharmacol. 11, 958. doi:10.3389/fphar.2020.00958

Park, S. H., Jang, S., Son, E., Lee, S. W., Park, S. D., Sung, Y. Y., et al. (2018). Polygonum Aviculare L. Extract Reduces Fatigue by Inhibiting Neuroinflammation in Stress-Restrained Mice. Phytomedicine 42, 180–189. doi:10.1016/j.phymed.2018.03.042

Perets, N., Hertz, S., London, M., and Offen, D. (2018). Intranasal Administration of Exosomes Derived from Mesenchymal Stem Cells Ameliorates Autistic-like Behaviors of BTBR Mice. Mol. Autism 9, 57. doi:10.1186/s13229-018-0240-6

Po, K. K., Leung, J. W., Chan, J. N., Fung, T. K., Sánchez-Vidaña, D. I., Sin, E. L., et al. (2017). Protective Effect of Lycium Barbarum Polysaccharides on Dextromethorphan-Induced Mood Impairment and Neurogenesis Suppression. Brain Res. Bull. 134, 10–17. doi:10.1016/j.brabull.2016.07.014

Prado, C. E., Watt, S., and Crowe, S. F. (2018). A Meta-Analysis of the Effects of Antidepressants on Cognitive Functioning in Depressed and Non-depressed Samples. Neuropsychopharmacol. Rev. 33, 32–72. doi:10.1016/j.nprv.2016.08.006

Qiu, Z. K., Zhang, G. H., Zhong, D. S., He, J. L., Liu, X., Chen, J. S., et al. (2017). Puerarin Ameliorated the Behavioral Deficits Induced by Chronic Stress in Rats. Sci. Rep. 7, 6266. doi:10.1038/s41598-017-06552-x

Rainville, J. R., Lipuma, T., and Hodes, G. E. (2022). Translating the Transcriptome: Sex Differences in the Mechanisms of Depression and Stress, Revisited. Biol. Psychiatry 91, 25–35. doi:10.1016/j.biopsych.2021.02.003

Ramshani, Z., Zhang, C., Richards, K., Chen, L., Xu, G., Stiles, B. L., et al. (2019). Extracellular Vesicle microRNA Quantification from Plasma Using an Integrated Microfluidic Device. Commun. Biol. 2, 189–9. doi:10.1038/s42003-018-0435-1

Ren, L., and Chen, G. (2017). Rapid Antidepressant Effects of Yueju: A New Look at the Function and Mechanism of an Old Herbal Medicine. J. Ethnopharmacol. 203, 226–232. doi:10.1016/j.jep.2017.03.042

Ruan, J., Liu, L., Shan, X., Xia, B., and Fu, Q. (2019). Anti-depressant Effects of Oil from Fructus Gardeniae via PKA-CREB-BDNF Signaling. Biosci. Rep. 39. doi:10.1042/BSR20190141

Ruan, X. F., Ju, C. W., Shen, Y., Liu, Y. T., Kim, I. M., Yu, H., et al. (2018a). Suxiaojin Juxin Pill Promotes Exosome Secretion from Mouse Cardiac Mesenchymal Stem Cells In Vitro. Acta Pharmacol. Sin. 39, 569–578. doi:10.1038/aps.2018.19

Ruan, X. F., Ju, Y. I., Ju, C. W., Shen, Y., Lei, W., Chen, C., et al. (2018b). Exosomes from Suxiaojin Juxin Pill-Treated Cardiac Mesenchymal Stem Cells Decrease H3K27 Demethylase UTX Expression in Mouse Cardiomyocytes In Vitro. Acta Pharmacol. Sin. 39, 579–586. doi:10.1038/aps.2018.18

Saeedi, S., Israel, S., Nagy, C., and Turecki, G. (2017). The Emerging Role of Exosomes in Mental Disorders. Transl Psychiatry 9, 122. doi:10.1038/s41398-019-0459-9

Salari, N., Hosseinian-Far, A., Jalali, R., Vaisi-Raygani, A., Rasoulpoor, S., Mohammadi, M., et al. (2020). Prevalence of Stress, Anxiety, Depression Among the General Population during the COVID-19 Pandemic: A Systematic Review and Meta-Analysis. Glob. Health 16, 57. doi:10.1186/s13438-020-0084-7

Schuh, M. A. P., Cuenca, J., Alcayaga-Miranda, F., and Khoury, M. (2019). Exosomes on the Border of Species and Kingdom Intercommunication. Transl. Res. 210, 80–98. doi:10.1016/j.trsl.2019.03.008

Song, Y., Sun, R., Ji, Z., Li, X., Fu, Q., and Ma, S. (2018). Perilla Alkyldehydro Attenuates CUMS-Induced Depressive-like Behaviors by Regulating TXNIP/TRX/NLRP3 Pathway in Rats. Life Sci. 206, 117–124. doi:10.1016/j.lfs.2018.05.038

Stenovec, M., Lasić, E., Božič, M., Bobnar, S. T., Stout, R. F., Grubišič, V., et al. (2016). Ketamine Inhibits ATP-Evoked Exocytotic Release of Brain-Derived Neurotrophic Factor from Vesicles in Cultured Rat Astrocytes. Mol. Neurobiol. 53, 6882–6896. doi:10.1007/s12035-015-9562-y
Stenovec, M., Li, B., Verkhrotsky, A., and Zorec, R. (2020). Astrocytes in Rapid Ketamine Antidepressant Action. Neuropharmacology 173, 108158. doi:10.1016/j.neuropharm.2020.108158

Su, J., Pan, Y. W., Wang, S. Q., Li, X. Z., Huang, F., and Ma, S. P. (2020). Saikosaponin-d Attenuated Lipopolysaccharide-Induced Depressive-like Behaviors via Inhibiting Microglia Activation and Neuroinflammation. Int. Immunopharmacol. 80, 106181. doi:10.1016/j.intimp.2019.106181

Sun, D., Zhuang, X., Xiang, X., Liu, Y., Zhang, S., Liu, C., et al. (2010). A Novel Nanoparticle Drug Delivery System: The Anti-inflammatory Activity of Curcumin Is Enhanced when Encapsulated in Exosomes. Mol. Ther. 18, 1606–1614. doi:10.1038/mj.2010.105

Sun, Y., Xu, X., Zhang, J., and Chen, Y. (2018). Treatment of Depression with Chai Hu Shu Gan San: a Systematic Review and Meta Analysis of 42 Randomized Controlled Trials. BMC Complement. Altern. Med. 18, 66. doi:10.1186/s12906-018-2130-z

Takeda, Y. S., and Xu, Q. (2015). Neuronal Differentiation of Human Mesenchymal Stem Cells Using Exosomes Derived from Differentiating Neuronal Cells. PLoS One 10, e0135111. doi:10.1371/journal.pone.0135111

Tavakolizadeh, J., Roshanaei, K., Salmaninejad, A., Yari, R., Nahand, J. S., Sarkarizi, H. K., et al. (2018). MicroRNAs and Exosomes in Depression: Potential Diagnostic Biomarkers. J. Cell. Biochem. 119, 3783–3797. doi:10.1002/jcb.25699

Théry, C., Witwer, K. W., Aikawa, E., Alcaraz, M. J., Anderson, J. D., Andriantsitohaina, R., et al. (2018). Minimal Information for Studies of Extracellular Vesicles 2018 (MISEV2018): A Position Statement of the International Society for Extracellular Vesicles and Update of the MISEV2014 Guidelines. J. Extracell. Vesicles 7, 1535750. doi:10.1080/20010378.2018.1535750

Topuçoğlu, A., and Ilgın, C. (2020). Mentalexo Approach for Diagnosis of Psychiatric Disorders. Med. Hypotheses 143, 109823. doi:10.1016/j.mehy.2020.109823

Upadhyay, R. K. (2014). Drug Delivery Systems. CNS protection, and the Blood Brain Barrier. Biomed. Res. Int. 2014, 869269. doi:10.1155/2014/869269

Valadi, H., Ekström, K., Bossios, A., Sjostrand, M., Lee, J. J., and Lötvall, J. O. (2007). Exosome-mediated Transfer of mRNAs and microRNAs Is a Novel Mechanism of Genetic Exchange between Cells. Nat. Cell Biol. 9, 564–569. doi:10.1038/ncl cell.2007.1596

Wallensten, J., Nager, A., Åsberg, M., Borg, K., Beser, A., Wilczek, A., et al. (2021). Leakage of Astrocyte-Derived Extracellular Vesicles in Stress-Induced Exhaustion Disorder: a Cross-Sectional Study. Sci. Rep. 11, 2009. doi:10.1038/s41598-021-81453-8

Wang, A. R., Mi, L. F., Zhang, Z. L., Hu, M. Z., Zhao, Z. Y., Liu, B., et al. (2018a). Resveratrol Ameliorates Restrain Stress-Induced Anxiety and Depression by Inhibiting HPA Axis Hyperactivity. Int. J. Mol. Sci. 19, 3468. doi:10.3390/ijms1913468

Wang, W., Liu, X., Liu, J., Cai, E., Zhao, Y., Li, H., et al. (2018d). Sesquiterpenoids from the Root of Panax Ginseng Attenuates Lipopolysaccharide-Induced Depressive-like Behavior through the Brain-Derived Neurotrophic Factor/Tropomyosin-Related Kinase B and Sirtuin Type 1 Nuclear Factor-KB Signaling Pathways. J. Agric. Food Chem. 66, 265–271. doi:10.1021/acs.jafc.7b04835

Wang, Y., Gao, C., Gao, T., Zhao, L., Zhu, S., and Guo, L. (2021b). Plasma Exosomes from Depression Ameliorate Inflammation-Induced Depressive-like Behaviors via Sigma-1 Receptor Delivery. Brain Behav. Immun. 94, 225–234. doi:10.1016/j.bbi.2021.02.004

Wang, Z., Zhang, D., Hui, S., Zhang, Y., and Hu, S. (2013b). Effect of Tribulus Terrestris Saponins on Behavior and Neuroendocrine in Chronic Mild Stress Rats. J. Tradit Chin. Med. 33, 228–232. doi:10.1016/j.jtcm.2012.05.024

Wei, Q., Zhou, W., Zheng, J., Li, D., Wang, M., Feng, L., et al. (2020a). Antidepressant Effects of 3-(3,4-Methylenedioxy-5-Trifluoromethyl Phenyl)-2e-Propanoic Acid Isobutyl Amide Involve TSPO-Mediated Mitophagy Signalling Pathway. Basic Clin. Pharmacol. Toxicol. 127, 380–388. doi:10.1111/bcpt.13452

Wei, Z. X., Xie, G. J., Mao, X., Zou, X. P., Liao, Y. J., Liu, Q. S., et al. (2020b). Exosomes from Patients with Major Depression Cause Depressive-like Behaviors in Mice with Involvement of miR-139-5p-Regulated Neurogenesis. Neuropsychopharmacology 45, 1050–1058. doi:10.1038/s41386-020-0622-2

Wheat, E. N. W., Stoye, D. Q., Cox, S. R., Wardlaw, J. M., Drake, A. J., Bastin, M. E., et al. (2020). DNA Methylation and Brain Structure and Function across the Life Course: A Systematic Review. Neurosci. Biobehav. Rev. 113, 133–156. doi:10.1016/j.neubiorev.2020.03.007

Wu, X. M., Gao, Y. B., Xu, L. P., Zou, D. W., Zhu, Z. Y., Wang, X. L., et al. (2017). Tongziluo Inhibits Renal Fibrosis in Diabetic Nephropathy: Involvement of the Suppression of Intercellular Transfer of TGF-[Formula: See Text]-Containing Exosomes from GECs to GMCs. Am. J. Chin. Med. 45, 1075–1092. doi:10.11201 sj02415X17050086

Xia, B., Huang, X., Sun, G., and Tao, W. (2021). Iridoids from Gardeniae Fructus Ameliorates Depression by Enhancing Synaptic Plasticity via AMPA Receptor-mTOR Signaling. J. Ethnopharmacol. 268, 113665. doi:10.1016/j.jep.2020.113665

Xiong, Z., Yang, J., Huang, Y., Zhang, K., Bo, Y., Lu, X., et al. (2016). Serum Metabonomics Study of Anti-depressive Effect of Xiao-Chai-Hu-Tang on Rat Model of Chronic Unpredictable Mild Stress. J. Chromatogr. B Analyt. Technol. Biomed. Sci. 1029-1030, 28–35. doi:10.1016/j.jchromb.2016.06.044

Xu, J. N., Chen, L. F., Su, J., Liu, Z. L., Chen, J., Lin, Q., et al. (2018). The Anzylolytic-like Effects of Ginsenoside Rg3 on Chronic Unpredictable Stress in Rats. Sci. Rep. 8, 7741. doi:10.1038/s41598-018-26146-5

Xu, Q., Jiang, M., Gu, S., Wang, F., and Yuan, B. (2020). Early Life Stress Induced DNA Methylation of Monoamine Oxidases Leads to Depressive-like Behavior. Front. Cell Dev. Biol. 8, 582247. doi:10.3389/fcell.2020.582247

Xu, H. Y., Yuan, T. J., Dad, H. A., Shi, M. Y., Huang, Y. Y., Jiang, Z. H., et al. (2021). Plant Exosomes as Novel Nanoplormas for MicroRNA Transfer Stimulate Neural Differentiation of Stem Cells In Vivo and In Vivo. Nano Lett. 21, 8151–8159. doi:10.1021/acs.nanolett.2c02530

Xu, Z. (2011). Modernization: One Step at a Time. Nature 480, S90–S92. doi:10.1038/408059a

Yang, J., Gao, F., Zhang, Y., Liu, Y., and Zhang, D. (2015). Buyang Huanwu Decoction (BYHWD) Enhances Angiogenic Effect of Mesenchymal Stem Cell by Upregulating VEGF Expression after Focal Cerebral Ischemia. J. Mol. Neurosci. 56, 898–906. doi:10.1007/s12031-015-0539-0
GLOSSARY

4-HNE 4-hydroxynonenal
5-HIAA 5-hydroxyindoleacetic acid
5-HT 5-hydroxytryptamine
8-OHdG 8-hydroxy-2′-deoxyguanosine
11β-HSD2 11β-hydroxysteroid dehydrogenase-2
ACTH adrenocorticotropic hormone
AKT protein kinase B
ASC Anti-TMS1
ATP adenosine triphosphate
Bax Bcl-2-associated X protein
BBB blood brain barrier
Bcl-2 B-cell lymphoma 2
BDNF brain-derived neurotrophic factor
CA1 the first region in the hippocampal circuit
CAT Catalase
CD36 cluster of differentiation 36
CD81 cluster of differentiation 81
CHM Chinese herbal medicine
CMS chronic mild stress
CMSC cardiac mesenchymal stem cells
CNS central nervous system
CORT CORT
COVID-19 coronavirus disease 2019
COX Cyclooxygenase
CRC colorectal cancer
CRH corticotropin-releasing hormone
CRP C-reactive protein
CRS chronic restraint stress
CSDS Chronic social defeat stress
CUMS chronic unpredictable mild stress
CUS chronic unpredictable stress
DCX doublecortin
DG dentate gyrus
DXM dextromethorphan
EAP experimental autoimmune prostatitis
EVs extracellular vesicles
FGF2 Fibroblast growth factor
FOXG1 Forkhead box transcription factor
FoxO1 forkhead box protein O 1
FST forced swimming test
GDNPs ginseng-derived nanoparticles
GFAP glial fibrillary acidic protein
GluA1 Glutamate Receptor 1
GPx Glutathione peroxidase
GR glucocorticoid receptor
GSH-pX glutathione peroxidase
HPA hypothalamic pituitary adrenal
Iba1 Ionized calcium binding adaptor molecule 1
IBA1 Ionized calcium binding adaptor molecule 1
IDO indoleamine 2,3-dioxygenase
IFN-γ interferon γ
IL-18 interleukin-18
IL-1β interleukin-1β
IL-34 interleukin 34
IL-6 interleukin-6
iNOS inducible nitric oxide synthase
IRS-1 insulin receptor substrate 1
IκB-α inhibitor of κB-α
JNK2 c-Jun NH2 terminal kinase
KIFC2 Kinesin Family Member C2
Kir4.1 inward rectifying potassium channel
LiCAM L1 Cell Adhesion Molecule
LDHA lactate dehydrogenase A
LH learned helplessness
LPS lipopolysaccharide
Maxim. Bolbostemma paniculatum
MCAO middle cerebral artery occlusion
MDA malondialdehyde
MDD major depressive disorder
miRNAs microRNAs
MKK4 mitogen-activated protein kinase kinase 4
NF-κB Nuclear factor kappa-light-chain-enhancer of activated B cells
NLRP3 oligomerization domain-like receptor family pyrin domain-containing 3
nNOS neural nitric oxide synthase
NO nitric oxide
NSCs neural stem cells
NSE Neuron-specific enolase
NT-3 Neurotrophin-3
p-AKT phosphorylation-akt
p-CREB phospho-CAMP response element-binding protein
PDK-1 pyruvate dehydrogenase lipoamide kinase isozyme 1
PI3K phosphoinositide 3-kinase
p-IκB phospho-inhibitor of kappa B
PMVs platelet-derived microvesicles
p-p65 anti-p-NF-κB p65
p-P70S6K Phospho-p70 S6 kinase
PSD-95 Postsynaptic density protein 95
ROS reactive oxide species
RS restraint stress
SDS social defeat stress
SERTs serotonin transporters
SGK1 glucocorticoid-regulated kinase 1
Sig-1R sigma-1 receptor
Sirt 1 sirtuin type 1
SOD superoxide dismutase
SRS spatial restraint stress
TBM1 tubeimoside-1
TCAs tricyclic antidepressants
TLR4 Toll Like Receptor 4
TNFR1 tumor necrosis factor receptor 1
TNF-α TNF-α
TrkB tropomyosin-related kinase B
TSPO translocator protein