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REVIEW ARTICLE

Research Progress of Essential Oil as a New Complementary Therapy in the Treatment of Depression

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Abstract: Depression is a mood disorder or affective disorder disease with depression as the main symptom. It has become a kind of mental disease that cannot be ignored in the world that seriously endangers human physical and mental health. Antidepressants commonly used in clinics generally have some defects, including slow action, unremarkable effects, and large side-effects. Therefore, there has a huge developing space for the research of new and effective therapeutic drugs to supplement or replace traditional drugs. The essential oil has obvious advantages in the treatment of depression and other emotional diseases, its aromatic odor can directly stimulate the olfactory nerves, and the lipophilic small- molecular compounds can cross the blood-brain barrier easily to play its regulatory role of releasing neurotransmitters and hormones related to depression, or adjusting the expression of brain-derived neurotrophic factor and proinflammatory cytokines. The pathogenesis of depression and the problems in traditional medication were illustrated, the research on the antidepressant effects and mechanism of essential oils in recent years is summarized, and the antidepressant chemical components in plant essential oils are reviewed in this article. The article provides scientific basis for an essential oil to be a new choice for relieving depression and treating depression.

Keywords: Depression, depressive disorder, essential oils, traditional antidepressants, animal models.

1. INTRODUCTION

Depression is characterized by depressed mood, manifested by psychological, behavioral, and physiological symptoms, including loss of interest in routine activities, energy loss, inattention, appetite loss, disturbed sleep, worthlessness, excessive guilt, and death or suicidal thoughts [1]. According to the estimation of the World Health Organization (WHO), depression affects more than 350 million individuals of all ages across the world [2, 3]. Depression has become the fourth most common disease worldwide, with an increasing number of suicidal deaths per year. Depression is becoming the second prevalent human disease after coronary heart disease. Therefore, it is of great significance to summarize the pathogenesis of depression and develop new drugs, to ensure people's healthy and normal quality of life (material and spiritual).

Essential oils (EOs), also known as volatile oils, or aromatic oils, are mostly aromatic oily liquids extracted from plants (flowers, buds, seeds, leaves, bark, herbs, wood, fruits, and roots). They are generally complex mixtures of natural compounds mainly composed of hydrocarbon (isoprene) and terpenoids and other molecules, such as aliphatic hydrocarbons, acids, alcohols, and other small molecules. Due to its wide range of anti-inflammatory, antibacterial, and antiviral activities [4-6], EOs are widely used in food [7, 8], cosmetics [9, 10], agriculture [11], and the pharmaceutical industry [12]. Notably, recent studies have reported the neurobiological activities of EOs such as sedation [13], analgesic [14], anti-epilepsy [15, 16], anti-anxiety [17, 18], anti-depression [19], and neuroprotection [20]. In recent years, because of their medicinal properties and fragrance, they are used to relieve stress and relieve emotions by the style of aromatherapy, and it has also been indicated that plant EOs serve as an alternative source for novel antidepressants [19]. The present study aimed to investigate the application of plant EOs in antidepressants and summarize the pathogenesis of depression.

2. THE MECHANISM OF DEPRESSION

2.1. Monoamine Hypothesis

The monoamine hypothesis is the first proposed mechanism of depression, illustrating that in the normal brain, monoamine neurotransmitters are released and bind to receptors on postsynaptic neurons, terminating transmission by re-

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ingesting the transmitter. In the event of depression, the decrease of monoamine concentration at the synapse site is considered to result in an emotional disorder [21], thus, suggesting that the decrease of 5-hydroxytryptamine (5-HT), dopamine, and noradrenaline levels in the synapse contributes to depression [22-27].

2.2. The Hypothesis of the Hypothalamic-pituitary-adrenal (HPA) Axis

The HPA axis is reported to be involved in the pathophysiological process of various emotional and cognitive disorders and is closely related to depression [28-32]. The changes in the HPA axis function in depression are attributed to the following factors:

① Increased corticotropin-releasing hormone (CRH) in cerebrospinal fluid [33, 34];

② Increased corticotropin secretion [35, 36];

③ Increased corticosterone and cortisol levels [37-39].

Further studies showed that the deleterious effects of corticoids could occur in the hippocampus and other brain nerves, mainly by binding to the Mineralocorticoid Receptor (MR) in the hippocampus and the Glucocorticoid Receptor (GR) in the stress-activated brain areas, such as the pituitary gland and the amygdala [39, 40]. The outcomes of excessive exposure to glucocorticoids range from the reversible atrophy of dendritic processes and inhibition of neurogenesis during acute exposure to frank neuronal death with chronic high-level exposure [41] (Fig. **1**).

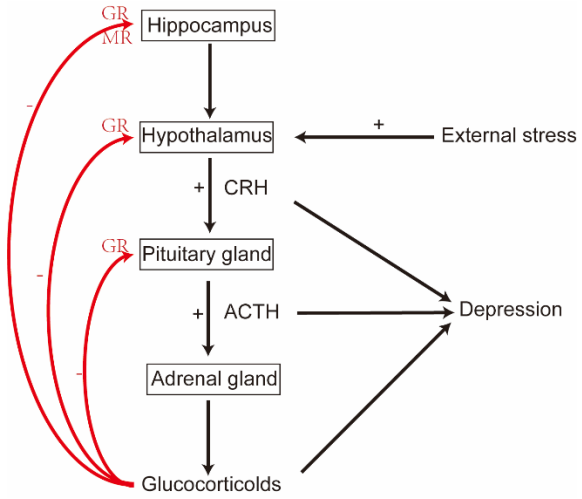

Fig. (1). Relationship between the HPA axis and depression.

CRH: corticotropin-releasing hormone; ACTH: adrenocorticotropic hormone; GR: glucocorticoid receptor; MR: mineralocorticoid receptor. +: stimulate; -: negative feedback.

2.3. Neurotrophic Hypothesis

Brain-derived neurotrophic factor (BDNF) is a kind of neurotrophic factor widely distributed in the hippocampus, cortex, cerebellum, and basal forebrain, along with is involved in other pathophysiological processes of neuropsychiatric diseases [42, 43]. Major depressive disorder was depicted as being secondary to deviant neurogenesis in brain regions that govern memory and emotion. Stress can reduce the expression of BDNF and lead to atrophy of hippocampal neurons [44]. Previously reported studies have shown the reduced expression of BDNF in the hippocampus of patients with depression [45, 46], thus making it a clinical indicator of some antidepressants [47-49].

2.4. Cytokines

Cytokines have the effect of causing depression, mainly by acting on the brain, causing changes in monoamine neurotransmitters, HPA axis, and neuroplasticity. Accumulating studies have highlighted the role of increased expression of proinflammatory cytokines, such as interleukin (IL-6), tumor necrosis factor-α (TNF-α), and IL-1β in eliciting depression [38, 50-52].

Moreover, Hyperpolarization-activated cyclic nucleotide-gated cation channels (HCN) [53] and TREK-1 channel [54, 55] also affect the occurrence of depression.

The fact that the exact mechanism of depression is not fully understood, therefore, the treatment of the depression based on its cause remained major challenging. Therefore, investigating antidepressant drugs with a rapid effect on the pathogenesis of depression is essential in the treatment of depression.

3.CLINICAL APPLICATION OF ANTIDEPRESSANTS

3.1. Function and Mechanism of Antidepressants

At present, the common antidepressants in clinical use are mainly based on the existing research on the pathogenesis of depression, according to the monoamine hypothesis, in which antidepressant effects are mainly manifested by an increase in the monoamine level in the synaptic cleft by the following ways [56]:

① Blocking the presynaptic monoamine transporters to remove the released transmitters from the extracellular space;

② Inhibiting degradation of monoamine neurotransmitters by monoamine oxidase (MAO);

③ Inhibiting or activating the presynaptic or postsynaptic receptors that regulate the release of monoamines and/or the rate of neuronal discharge.

Additionally, these drugs include monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAS), selective 5-HT reuptake inhibitors (SSRIs), and 5-HT-serotonin and noradrenaline reuptake inhibitors (SNRIs) [57-59]. Monoamine oxidase-A (MAO-A) is a therapeutic target for neurodegenerative diseases and emotional disorders [60]. Monoamine oxidase-B (MAO-B) is an important high-density enzyme in the brain, which exists in neurons and astrocytes. It produces oxidative stress, alters mitochondrial function, and metabolizes 5-hydroxytryptaminergic chemical compounds through hydrogen peroxide release [61]. Besides,

the level of MAO-A transcription activator Kruppel-like factor 11 (KLF11) has been reported to increase in stressed mice [62]. MAO inhibitors decrease the oxidative metabolism of monoamine neurotransmitters and thus increase the monoamine level in synapses by inhibiting the activity of MAO. Moreover, 5-HT transporter (SERT) and adrenergic receptor are known as the main regulators of 5-HT level and noradrenaline in the brain, and the main targets of TCAs, SSRIs, and SNRIs [63-65]. Whilst Tricyclic antidepressants demonstrate their antidepressant effect by downregulating the activity of α2-adrenergic receptors (ARs), 5-HT_{1A} receptor, and 5-HT_{2A} receptor in the presynaptic membrane while blocking the reuptake of noradrenaline and 5-HT in noradrenergic and 5-hydroxytryptaminergic nerve endings [63, 64, 66].

3.2. Disadvantages of Commonly used Antidepressants in Clinics

The fact that traditional antidepressants have a single target and delayed onset of efficacy; therefore, only a few patients with depression get good relief after receiving antidepressants. On the other hand, patients exhibit a variety of adverse reactions [67-69], such as 5-HT syndrome [70-73], cardiovascular side effects [74], gastrointestinal side effects [75, 76], anticholinergic effects [69, 74, 77] and others. Accordingly, MAOIs and TCAs are first-generation antidepressants. The most common early side effects of MAOIs include postural hypotension, dizziness, drowsiness, insomnia, and nausea [78, 79]. Moreover, MAOIs can react with a large amount of tyramine in foods and ultimately leads to a fatal hypertension crisis [80], which limits the clinical use of MAOIs. At present, MAOIs are mainly used as second-line drugs for the treatment of depression that tricyclic or other drugs have failed to treat. Whilst the major disadvantages of TCAs are the slow onset of efficacy and side effects of anticholinergic action such as dry mouth, constipation, urinary retention, blurred vision, and elevated intraocular pressure. Besides, it has also cardiovascular toxicity, especially for elderly patients, which can lead to arrhythmia, orthostatic hypotension, atrioventricular block, myocardial infarction, and heart failure [74, 77]. Therefore, the use of TCAs is limited in elderly and depressed patients with heart disease. Although compared with TCAs, SSRI, and SNRIs have fewer side effects, such as cardiovascular adverse reactions [67, 74 and 81]. However, SSRIs and SNRIs may induce suicidal thoughts in adolescents [82-84], while SSRIs have been reported to increase the risk of spontaneous intracranial hemorrhage (ICH) [85]. Collectively, developing and investigating more safe and effective novel antidepressants are urgently required. Therefore, novel antidepressants are widely concerned and developing novel antidepressants, especially from the plant extracts, may become a new development trend of antidepressants.

4. RESEARCH PROGRESS OF NATURAL PLANT EOS IN ANTIDEPRESSANT TREATMENT

Plant EOs is rich in bioactive molecules, holding promise for the development of new antidepressants [86-89]. A variety of EOs showed antidepressant effects on multiple animal models of antidepressants. These animal models include not only the classic primary screened models such as Forced Swimming Test (FST), Tail Suspension Test (TST), and open-field test (OFT) [90, 91], but also the highly-recognized chronic unpredictable mild stress (CUMS), in addition to spared nerve injury (SNI) and corticosterone-induced models [92, 93], indicating the accurate and reliable antidepressant activity of plant EOs. Furthermore, clinical experiments have confirmed that the treatment of lavender EOs (Silexan) significantly reduces the Hamilton Depression Rating Scale (HAMD) score [94] while anise oil markedly decreases the Beck Depression Inventory (BDI) score [95], providing further clinical evidence for the anti-depression effect of EOs.

Among the existing literature of antidepressant mechanisms, some are based on the classic monoamine hypothesis [90, 96-101], some on the stress-induced HPA axis hypothesis [91, 92, 102, 103], and some on the neurotrophic hypothesis [91, 97, 104-107]. Collectively, suggesting that the plant EOs possess the multi-system activity and exhibit antidepressant effect through multi-target cooperation.

4.1. The Natural Advantages of Antidepressant Effects of Essential Oils

Emotions are controlled by different parts of the brain, while depression is a kind of emotions, The researches of molecular neurobiology of depression showed that these brain regions are related to the pathophysiology of depression as illustrated in Fig. (**2**) [108]. While the olfactory pathway of human was as follows, when the smell was identified by the specific gas receptors on the membrane of olfactory epithelial sensory neurons, it will transmit them along the axons of olfactory sensory neurons to the olfactory bulb, which projects the incoming signals to the primary olfactory cortex. After the signals were connected with the neurons in the olfactory cortex and the olfactory bulb, they were transmitted to the anterior olfactory nucleus, piriform cortex, hypothalamus, amygdala, and medial olfactory cortex of the primary olfactory cortex, and they were transmitted to the hippocampus through the secondary olfactory cortex of the olfactory center. The aromatic smell of plant essential oil can directly stimulate the olfactory nerve and quickly regulate brain function, meanwhile, the small molecule liposoluble substance of essential oil is easy to pass through the blood-brain barrier, which overcomes the problem that traditional antidepressants are difficult to enter the brain. So we think that the material basis of essential oil and its special application method makes it have a good advantage in antidepressant treatment.

4.2. Research Trend of the Antidepressant EOs

In the present study, a total of 53 literature on the antidepressant plant EOs in the past 20 years were retrieved from the PubMed website with “depression”, “depressive disorder”, and “oil, volatile” as the keywords (Fig. **3**). Literature retrieval showed an increasing number of literature on the antidepressant plant EOs in five years, indicating that the anti-depression effect of EOs had gained more attention in the past 20 years. However, the total number of literature remained fewer, suggesting that the antidepressant research of EOs is still at an early stage of exploration, and a more

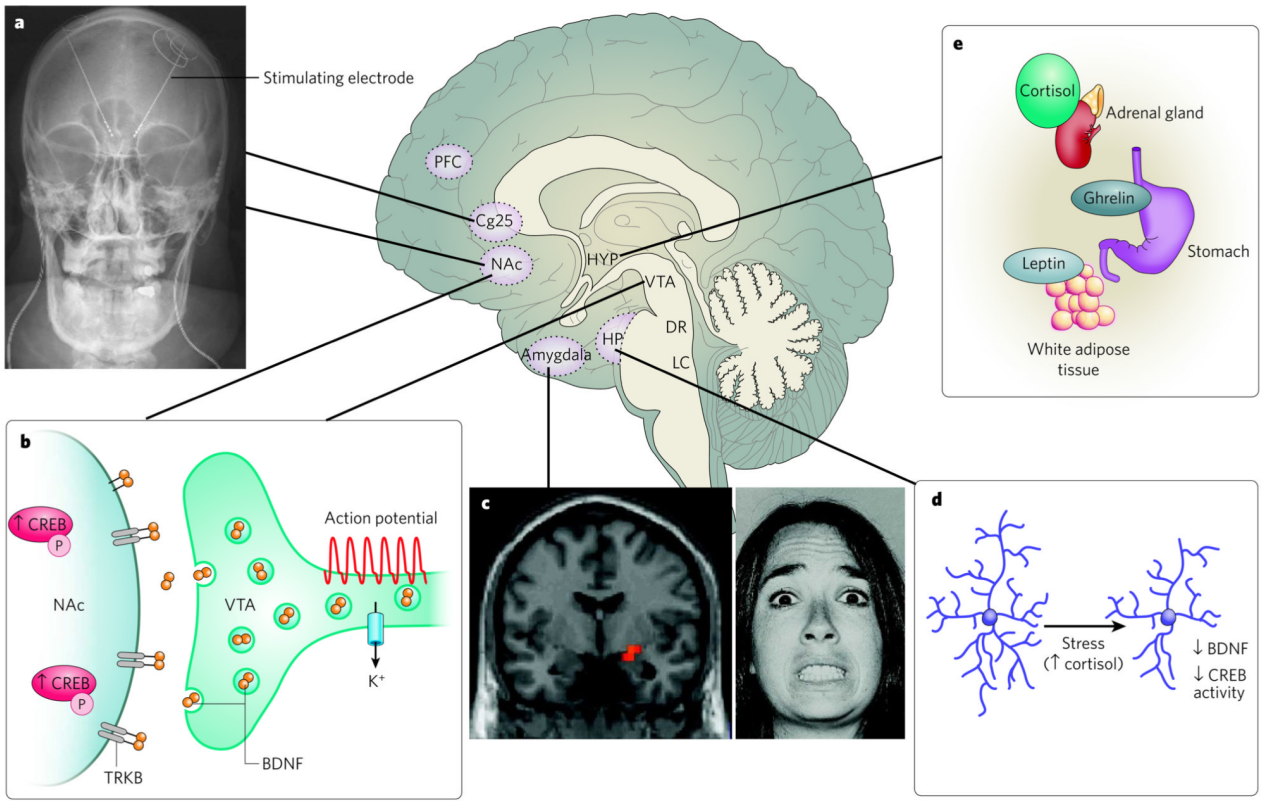

Fig. (2). Neural circuitry of depression. **a**, Deep brain stimulation of the subgenual cingulate cortex (Cg25) or the nucleus accumbens (NAc) has an antidepressant effect on individuals who have treatment-resistant depression. **b**, Increased activity-dependent release of brain-derived neurotrophic factor (BDNF) within the mesolimbic dopamine circuit (dopamine-producing ventral tegmental area (VTA) to dopamine-sensitive NAc) mediates susceptibility to social stress. **c**, Neuroimaging studies strongly implicate the amygdala (red pixels show activated areas) as an important limbic node for processing emotionally salient stimuli, such as fearful faces. **d**, Stress decreases the concentrations of neurotrophins (such as BDNF) and induces the damage of neuronal cells. **e**, Peripherally released metabolic hormones in addition to cortisol, such as ghrelin and leptin, produce mood-related changes through their effects on the hypothalamus (HYP) and several limbic regions (for example, the hippocampus, VTA and NAc). DR, dorsal raphe; LC, locus coeruleus; PFC, prefrontal cortex [108]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

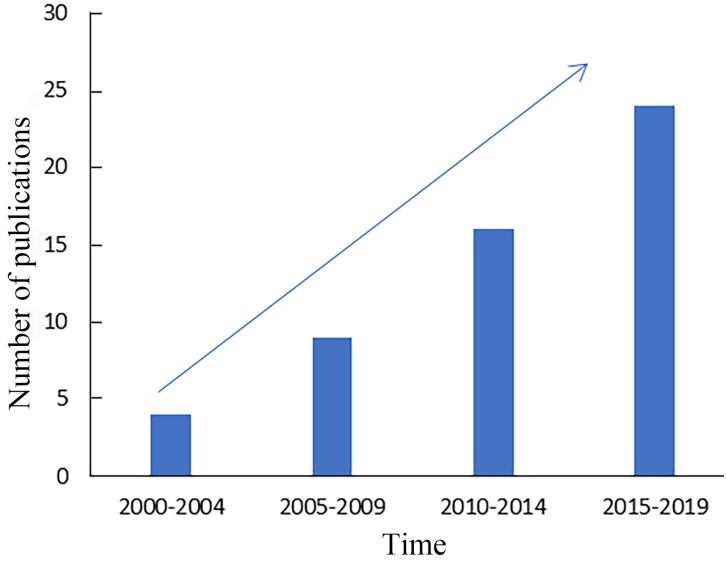

Fig. (3). Publications on antidepressant research of essential oils in the past two decades. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. Aromatic plant essential oils studied in experimental depression in the past five years.

Plant Species	Essential Oil Component	Administration *via* and Duration of Treatment	Behavioral Test	Observed Effect	Ref.
***Pelargonium roseum* Willd**	monoterpene alcohols citronellol (35.9%) and geraniol (18.5%)	Intraperitoneal administration	EPM OFT FST	+ + +	[90]
***Ocimum basilicum* Linn.**	linalool (35.9%), 1,8-Cineole(11.2%), α-cadinol(11.4%), farnesyl acetate (10.2%)	Inhalation	FST EPM OFT	+ + +	[91, 104, 105]
Toona ciliata* Roem. *var. yunnanensis	estragole (6.16%), β-elemene (24.91%), β-cubebene (14.29%), and γ-elemene (8.05%)	Oral	FST TST OFT	+ + -	[97]
***Liquidambar orientalis* Mill**	benzoic acid, benzyl benzoate, benzyl cinnamate, cinnamic acid cinnamate	Inhalation	TST FST SPT	+ + +	[114-116]
Syzygium aromaticum	eugenol (88.58%), eugenyl acetate (5.62%), β-caryophyllene (1.39%), 2-heptanone (0.93%), ethyl hexanoate (0.66%), humulenol (0.27%), α-humulene (0.19%), calacorene (0.11%) and calamenene (0.10%).	Oral	FST TST SPT	+ + +	[106]
Asarum heterotropoides	methyl eugenol (22.58%), pentadecane (6.78%), 2,3,5-trimethoxytoluene (5.54%), 4-(chloromethyl) cyclohexene (3.36%), myristicine (3.27%), sesamin (3.24%), and kakoul (2.63%).	Inhalation	FST TST	+ +	[98]
Radix et Rhizoma Asari	eugenol-methyl ether(60%), Safrol(8%),Asatone(6%)Cis-Asarone(2%)	Oral	FST TST OFT	+ + -	[121]
***Lavandula augustifolia* Mill.**	linalyl acetate(36.55%), linalool(31.17%), cis-β-ocimene(3.33%), lavandulyl acetate(1.86%), 1-Octen-3-yl acetate(1.64%), 1,8-cineole(1.46%), camphor(0.53%)	Inhalation	FST	+	[92, 123]
***Citrus sinensis* (L.) Osbeck**	d-limonene(92.81%), α-pinene(2.32%), β-pinene(2.22%), γ-terpinene(2.239%), α-phellandrene(0.12%), 1,3,8-p-menthatriene(0.18%), ocimene(0.05%), and 1,4-dimethylene cyclohexane(0.01%).	Inhalation	OFT FST SPT	+ + +	[135, 141]
Chamaemelum nobile	Isobutyl angelate and Iso-amyl methacrylate(34.53%), Angelic acid isoamyl ester(15.86%), Limonen (1.74 %), Alpha-pinene(1.68%)	Inhalation	OFT FST	+ +	[137-138]
Citrus bergamia	linalool(10.86%), linalyl acetate(18.57%), limonene(26.70%)	Inhalation	FST	+	[107]
Agarwood	aromatics (24.114%), including 7-methyltridecane (11.228%), pyrethrone (2.316%) and perhydropyrene (1.619%)	Inhalation	TST FST	+ +	[103]

FST: forced swimming test; TST: tail suspension test; OFT: open field test; EPM: elevated plus-maze; SPT: sucrose preference test; +: antidepressant-like effect; -: no significant difference.

comprehensive research basis is urgently required to achieve a breakthrough.

4.3. Relevant Studies on the Antidepressant Effect of Plant EOs

In recent years, several kinds of plant EOs are being used in antidepressant treatment:

As summarized in Table **1**, the following essential oils of plants displayed some antidepressant-like effects when tested in rodents.

4.4. *Pelargonium Roseum* Willd

In the previously reported research, swiss albino male mice following depression modeling were intraperitoneally injected with 10, 20, and 50 mg/kg *Pelargonium roseum* oil and subsequently subjected to the behavior test. The results showed that the *P. roseum* oil effectively increased the total number and time in the open arms in mice exposed to the elevated plus-maze (EPM) while reduced the exploration behavior during OFT and the immobility time during FST. Besides, the pretreatment of WAY-100635 (a selective 5-HT1A receptor antagonist) instead of flumazenil (a benzodiazepine antagonist) was found to reverse the role of EO in EPM and FST, indicating that the anti-anxiety and antidepression activities of EO are transmitted through serotonergic energy rather than GABAergic energy [90].

4.5. *Ocimum basilicum* Linn

Ocimum basilicum essential oil (EOOB) has a sedative effect [109, 110] and studies have shown that its inhibitory effect on the excitability of the peripheral nervous system is due to the presence of (-)-linalool in the EOOB [111].

Accordingly, in previously reported work, Syrian male mice were injected with 100, 150, 200 mg/kg of water-alcohol extract and 200 mg/kg of EOOB, and then subjected to EPM. The results revealed a significant increase in the arm extension time ($p < 0.05$) in mice injected with water-alcohol extract and EO (75.8% [$p < 0.001$]) as compared with those in the control group [112]. Moreover, a decreased time during the FST and increased activities during the OFT were found. Inhalation of EOOB has been reported to improve the depression caused by CUMS [91, 104-105]. Whilst growing studies have revealed the possible antidepressant mechanism of basil oil by which EOOB can reduce the increased serum corticosterone ($p < 0.001$) and glucocorticoid receptors (GRs) induced by CUMS, upregulate the level of hippocampal protein and BDNF, reduce the CUMS-induced neurodegenerative & atrophic changes in the hippocampus, and increase the number of astrocytes and newborn nerve cells [91, 104,105].

4.6. *Toona sinensis (A. Juss.)* Roem

Toona sinensis has significant anti-inflammatory activity. Polyphenols from *Toona sinensis* seeds (PTSS) has been reported to protect dopamine (DA) neurons (tyrosine hydroxylase (TH)-positive) in the substantia nigra of rats by inhibiting the p38MAPK signaling pathway and reducing the expression of inflammatory factors [113]. Intriguingly, it has been indicated that the treatment of neurodegenerative diseases with *Toona sinensis* leaf extract (TSL)-1 significantly inhibit the lipopolysaccharide (LPS)-induced NO production, TNF-α secretion, and inducible nitric oxide synthase (NOS) protein expression in a concentration-dependent manner, and suppresses the BV-2 microglia which further repress the production of activated inflammatory mediators from the microglia [114]. Whilst *Toona sinensis* EO with different concentrations were used to treat CMS rats, and the results of FST and TST showed that EO at a dose of 10, 20, 40, and 80 mg/kg could significantly reduce the immobility time, but no walking alterations were observed in the OFT. Additionally, treatment with 20, 40, and 80 mg/kg of *Toona sinensis* EO has been demonstrated to increase the content of DA, noradrenaline, 5-HT, and BDNF in the hippocampus of CMS rats [97].

4.7. *Liquidambar Orientalis* Mill

Previously reported studies have illustrated that the mice undergoing acute stress and CMS exhibited shortened residence time in the central compartment during the OFT, prolonged feeding latency in the novelty-suppressed feeding (NSF) test, and reduced sucrose preference value in the sugar preference test (SPT) and immobility time in the FST and TST. The above-described parameters returned to normal level after sniffing the oil of *Liquidambar orientalis* Mill. (Styrax), indicating that the depression of acute stress and CMS mice could be relieved by the Styrax oil [116, 117].

Accordingly, the serum levels of angiopoietin (ANG), thrombopoietin (TPO), IL-6, and TNF-α were measured by enzyme-linked immunosorbent assay (ELISA) and its results showed that inhalation of Styrax reduced the serum levels of ANG, TPO, IL-6, and TNF-α in mice exposed to acute stress while the levels of ANG and TPO were reduced in mice exposed to CMS. On the other hand, Styrax has been reported to mediate these effects by regulating the inflammatory response and reducing the angiogenesis dysfunction and thrombosis [116].

4.8. *Syzygium aromaticum* (L.) Merr. & Perry

Previously reported evidence has shown that Eugenia brasiliensis, Eugenia catharinae, and Eugenia umbelliflora of the genus Syringa play an antidepressant role in TST, which seems to be mediated by 5-HT1A and 5-HT2 receptors, noradrenaline (α1-adrenergic receptor) and dopaminergic (dopamine D1 and D2 receptors) systems [118]. Another study has shown significant antidepressant effects of the *S. aromaticum* EO following the FST (200 mg/kg, $p < 0.05$) and TST (100 and 200 mg/kg, $p < 0.05$). Long-term administration of the *S. aromaticum* EO remarkably increased sucrose preference in CMS mice (50 mg/kg, $p < 0.05$; 100 and 200 mg/kg, $p < 0.01$), and upregulated the protein level of BDNF and the extent of ERK and CREB phosphorylation in the hippocampus [106].

4.9. *Asarum sieboldii Miq*

Asarum decoction has been documented to reduce the level of phosphorylated at p-thr231 and p-ser422 sites in the hippocampus of rats, thus preventing the pathological process of Alzheimer's disease [119]. Mahuang Fuzi Asarum

decoction has been indicated to improve the depression-like behavior provoked by LPS from Gram-negative bacteria in mice, manifested by significantly increased expression of Nod-like receptor protein 3 (NLRP3), caspase-1p20, ASC, and thioredoxin-interacting protein (TXNIP), diminished expression of IL-1β and augmented expression of BDNF and myosin-related kinase B, BDNF receptor, in the hippocampus [120].

Consistently previously reported studies have indicated that Asarum EO and high/medium/low-dose (2, 1, 0.5 g/mL) of Asarum decoction were used in the treatment of depression in mice. The high-dose Asarum decoction and Asarum EO was observed to decrease the immobility time of mice in the TST (high dose $p < 0.01$, EO $p < 0.01$) while Asarum decoction and EO reduced the immobility time of FST ($p < 0.05$) and elevated the content of GABA ($p < 0.01$), Glu ($p < 0.05$) and 5-HT (medium dose $p < 0.01$; low dose $p < 0.05$) in mouse brain. Hence, indicating that Asarum decoction and EO were demonstrated to possess antidepressant effects for the first time [121]. Besides, Asarum EO markedly reduced the expression of CRF positive neurons in the paraventricular nucleus, TH-positive neurons in the locus coeruleus, and 5-HT positive neurons in the dorsal raphe nucleus [98].

4.10. *Lavandula angustifolia* Mill.

Existing reviews have systematically summarized the anti-depression effects of lavender essential oil (LEO) [122], which may have multi-faceted mechanisms of action, as well as the two-way effect on neuroregulation.

The neuroprotective effect of LEO on scopolamine-induced dementia rat models and oxidative stress in the brain [124, 125] may be derived from the antioxidant and anti-apoptosis activities of LEO [124]. Moreover, previous studies have suggested LEO is involved in neurotransmission by interacting with the 5-HT_{1A} receptor [126] and dopamine receptor in the olfactory bulb [127]. LEO can also affect the function of the paraventricular nucleus of the hypothalamus, dorsomedial nucleus of the hypothalamus, and central nucleus of the amygdala [128, 129]. In the LEO group, the time spent floating on the FST was decreased compared with the control group, which indicates the decreased depression-like behavior [92]. It has been found that the anti-anxiety mechanism has been correlated with the regulation of BDNF [92, 130].

4.11. *Rosa rugosa* Thunb.

Rose oil has widely been known for its significant neurobiological activity, which can reduce sympathetic nerve activity by 40% and plasma adrenaline concentration by 30% [131]. Acute subcutaneous injection or chronic oral administration of rose oil and Geranium oil can largely shorten the immobility time of mice in the FST, while this antidepressant activity has been suggested being mediated by a presynaptic mechanism [132]. Another study has suggested after inhaling 2-phenyl ethanol (2-PE; the main component of rose oil), the mice spent less time on the central area and the immobility time in the OFT and TST; however, the cognitive function, activity, muscle strength, or aggression were not altered [133]. Therefore, it was suggested that 2-PE could cause neuropsychological effects of changing mouse behaviors. The flavonoids contained in the rose oil, including free radical antioxidants such as rutin and quercetin [134] may also provide a theoretical basis for using rose oil as a treatment of depression.

4.12. *Citrus sinensis (L.)* Osbeck

Orange [*Citrus sinensis* (L.) Osbeck] essential oil (OEO) has been used in aromatherapy for depression. However, limonene and monoterpenes have been demonstrated to directly function in the central nervous system and olfactory nerve, thus influencing emotion. Moreover, the CUMS-induced depression-like behavior could be improved in mice upon OEO inhalation, characterized by decreased bodyweight, sucrose preference, curiosity, and mobility as well as shortened immobile time and attenuated dyslipidemia. Whilst limonene exhibited the highest content in the brain following OEO inhalation, and it was not immediately metabolized in the brain. Notably, inhalation of limonene has been reported to ameliorate depression-like behavior caused by CUMS, the hyperactivity of the HPA axis, reduce the level of monoamine neurotransmitters, and the expression of BDNF and its receptor in the hippocampus. Furthermore, OEO can affect the NADPH-d positive cells and the activity of NOS in the cerebral cortex and possess an effect through nitration neurotransmission [136].

4.13. *Chamaemelum Nobile*

Consistently, in a previously reported behavior experiment of stress-induced animals treated with *Chamaemelum nobil* (Roman chamomile) and clomipramine, a significant decrease was found in the immobility time during the FST, confirming the antidepressant effect of the combination of chamomile and clomipramine and revealing its antidepressant role by downregulating the level of corticosterone via the HPA axis and then enhancing the hippocampal neurogenesis [137]. Another study enrolling the Rattus norvegicus and Wistar-Kyoto (WKY) rats found that Roman chamomile and its main component *i.e.*, α-pinene, could alleviate the depression-like behavior of rats in the FST by aromatherapy for two weeks [138]. Besides, the results from isobaric-tags for relative and absolute quantitation (iTRAQ) technique demonstrated that the expression of proteins related to oxidative phosphorylation was increased in the brain of WKY rats treated with α-pinene, including cytochrome C oxidase 6C-2 subunit, and 7A2 subunit, ATPase inhibitor in the hippocampus, and cytochrome C oxidase 6C-2 subunit, ATP synthetase e-subunit, acyl carrier protein and cytochrome b-c1 complex subunit 6 in the prefrontal cortex. Reverse transcription-quantitative real-time polymerase chain reaction (RT-qPCR) also found that the mRNA expression of parvalbumin was elevated in the hippocampus of WKY rats upon aromatherapy treatment using α-pinene, while iTRAQ analysis showed that the expression was up-regulated by 2.8 folds in the hippocampus [138].

4.14. *Citrus medica* L. var. *sarcodactylis* Swingle

Citrus medica L. var. sarcodactylis Swingle (Bergamot) essential oil (BEQ) has been indicated to possess great neu-

robiological activity [139]. It can affect synaptic transmission, regulate electroencephalogram, show neuroprotective and analgesic effects, and treat schizophrenia [140]. A previously reported study has revealed the effects of limonene on GABA, 5-hydroxyindoleacetic acid (5-HIAA), and 5-HT and it can inhibit HPA activity under physiological stress, which may play an anti-stress role through GABA(A) receptor [142]. During the behavioral tests, mice treated with BEQ presented with reduced immobility time [107, 143], crossing, rearing, and wall rearing [130], and increased percentage of time to times of the open arms [140, 142], which confirmed the anti-depression effects of BEQ, with a potentially dose-dependent increase [144]. In addition to that, BEQ could reduce the response of stress to corticosterone [141] and improve the extracellular level of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the hippocampus [145] but another research indicated that BEQ did not affect the response to the HPA axis and BDNF protein expression in chronic restraint stress (CRS) [107].

4.15. Agarwood

The aromatic compounds of Agarwood are sesquiterpenes and chromone derivatives and the main sources of the special smell of Agalloch. Increasing evidence has demonstrated the sedative and antidepressant activities of AEO [103, 146, 147].

In the stress-induced mouse model, the results of the TST and FST revealed decreased immobility time, indicative of antidepressant effects of AEO. Moreover, pressure can lead to an increase of cytokines and NO and further induce the hyperactivity of the HPA axis. AEO attenuated the serum levels of IL-1α, IL-1β, and IL-6 in a dose-dependent manner, thereby markedly reducing the mRNA expression of nNOS in the cerebral cortex and inhibiting the protein expression of nNOS in the hippocampus. Measurement on the upstream regulatory factors corticotropin-releasing factor (CRF) and its receptor CRFR of the HPA axis presented that AEO greatly reduced the gene expression of CRF, the gene transcription, and protein expression of CRFR in the cerebral cortex and hippocampus. Additionally, the concentration of adrenocorticotropic hormone (ACTH) and corticosterone in downstream of the HPA axis, as measured by ELISA, was also decreased by AEO in a dose-dependent manner. Taken together, these results demonstrated that the anti-anxiety and anti-depression role of AEO correlates to the hyperactivity inhibition of CRF and the HPA axis [103].

CONCLUSION

Pharmacological studies have confirmed the antidepressant potentials of EOs as a novel antidepressant. Nonetheless, the diversity of active chemical components in EOs can be an advantage in the treatment of depression as the chemical compounds exert synergistic effects and also act on multiple targets, thus playing an antidepressant role. However, at present, except for the lavender EOs and their preparation *i.e.*, silexan has been widely applied in clinical trials [147, 148], whereas other EOs have no optimistic outlook in clinical application, indicating that the treatment of antidepressant with EOs is still in the primary stage. Future studies are warranted to provide scientific support for EOs as a treatment option for depression based on a large number of clinical trials.

In the current studies (Table **1**), the modes of administration of antidepressant animal models are inhalation, oral and intraperitoneal. But based on the understanding of the security of essential oil and most components of essential oils are small molecular fat-soluble substances that are easily passed through the blood-brain barrier, we think sniff might be a fast, safe and effective way for essential oil antidepressant therapy. When the other administration methods were used in the study, the safety of essential oil should be considered.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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