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REVIEW ARTICLE

Linalool as a Therapeutic and Medicinal Tool in Depression Treatment: A Review

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Abstract: Depression is a prevalent disease worldwide, limiting psychosocial functioning and the quality of life. Linalool is the main constituent of some essential oils from aromatic plants, representing about 70% of these volatile concentrates. Evidence of the linalool activity on the central nervous system, mainly acting as an antidepressant agent, is increasingly abundant. This review aimed to extend the knowledge of linalool's antidepressant action mechanisms, which is fundamental for future research, intending to highlight this natural compound as a new antidepressant phytomedication. A critical analysis is proposed here with probable hypotheses of the synergic mechanisms that support the evidence of antidepressant effects of the linalool. The literature search has been conducted in databases for published scientific articles before December 2020, using relevant keywords. Several pieces of evidence point to the anticonvulsant, sedative, and anxiolytic actions. In addition to these activities, other studies have revealed that linalool acts on the monoaminergic and neuroendocrine systems, inflammatory process, oxidative stress, and neurotrophic factors, such as BDNF, resulting in considerable advances in the knowledge of the etiology of depression. In this context, linalool emerges as a promising bioactive compound in the therapeutic arsenal, capable of interacting with numerous pathophysiological factors and acting on several targets. This review claims to contribute to future studies, highlighting the gaps in the linalool knowledge, such as its kinetics, doses, routes of administration, and multiple targets of interaction, to clarify its antidepressant activity.

Keywords: Linalool, neuropharmacological effects, therapeutic effects, antidepressant bioactive compound, depression, essential oils.

1. INTRODUCTION

Depression is a prevalent disease worldwide, limiting psychosocial functioning and the quality of life. The disease is a mood disorder that displays repeated depressive episodes, characterized by several symptoms, including depressed mood, loss of interest and anhedonia (loss of pleasure), anxiety symptoms, disturbed sleep and appetite, guilt and low self-esteem, and poor concentration [1].

The pathophysiological mechanism of depression is not yet fully elucidated. However, the involvement of decreased monoaminergic neurotransmitters or modified monoaminergic receptors, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, inflammatory process, oxidative stress, and neuroplasticity dysfunction have been historically confirmed. Furthermore, the potential indirect involvement of the glutamatergic pathway in the etiology of this psychiatric disease has also been pointed [2, 3].

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Clinical and pre-clinical studies that include aromatherapy with essential oils rich in linalool and their potential interaction with the various factors involved in the pathophysiology of depressive disorders have been reported. Evidence of the action of linalool in the central nervous system (CNS), mainly acting as an antidepressant agent, is increasingly abundant [4-6]. Several studies have shown that aromatherapy based on linalool-rich essential oils, such as lavender (*Lavandula angustifolia* Mill.), bergamot (*Citrus bergamia* Risso), and orange (*Citrus sinensis* L.) improves mood and reduces symptoms of stress, anxiety, and depression of patients submitted to surgeries, invasive methods, endoscopic exams, hemodialysis, and dental procedures [7]. Besides, in human studies, linalool and its enantiomers have been investigated according to the physiological and mood-altering effects of essential oils fragrances. The data revealed that both ylang ylang essential oil (*Cananga odorata* Hook.) and linalool have “harmonizing” effects. The oils of peppermint (*Mentha piperita* L.) and spearmint (*Mentha spicata* L.), which presents lower concentrations of linalool, also displayed this same effect [8]. Thus, the knowledge of linalool's antidepressant action mechanisms is fundamental for future research, intending to highlight this natural compound as a new antidepressant phytomedication [9].

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2. MATERIALS AND METHODS

Scientific information about depression, the pathophysiological factors and the action of linalool on these factors, other biological activities of linalool, and its natural sources were retrieved from the online bibliographic databases, including Web of Science, Scopus, Springer Link, Google Scholar, PubMed, and Science Direct. The keywords used include linalool, depression, pathophysiological factors, monoaminergic system, stress, HPA axis, neuroendocrine system, inflammatory process, oxidative stress, Brain-Derived Neurotrophic Factor (BDNF), biological activities, natural sources, and other related words. Several literature articles published before December 2020 were consulted. Secondary resources were also analyzed, like books and proceedings.

3. MOLECULAR ASPECTS OF DEPRESSION

The pathogenesis of depression may present multifactorial causes, mainly dysregulation of numerous neurotransmitters and metabolic systems. In this context, monoaminergic neurotransmitters, HPA axis, inflammatory process, oxidative stress, and neurotrophic factors appear in a prominent position in the etiology of the disease and continue to be the focus of several studies [3, 10].

Concerning the monoamines theory, serotonin and norepinephrine play a pivotal role in the pathophysiology of this psychiatric disorder. There is clear evidence of reduced availability of tryptophan, the precursor to serotonin, and changes in healthy physiological metabolism and serotonin level receptors may elicit depression. In addition to serotonin, noradrenergic dysfunction has been closely related to depression disease. Thus, several drugs currently used to treat depressive states present the pharmacological objective of increasing the monoamines levels on the synaptic cleft through the norepinephrine reuptake inhibitors, with minimal effect on serotonin receptors [11], or acting on both receptors with similar affinity [3]. Evidence of dopaminergic system involvement in depression is less noted compared to the serotonergic/noradrenergic pathway. However, dopamine effects have been related to mood regulation, reward system, and motivational circuitry. Thus, in clinical practice, specific antidepressant agents increase dopamine levels in the brain by inhibiting dopamine reuptake or acting as a dopaminergic receptor agonist [12].

The involvement of environmental stress and severe life events in the development of depression is also well documented [13]. Stress and depression share several mediators and circuitry that interfere with the clinical course of the disease [14]. Thus, protection against the onset of depression can occur with the absence of stress. Therefore, deregulation of the stress response, displaying morphofunctional changes in the CNS, can trigger depression [14]. Stress information is recognized in the cerebral cortex, which follows the hypothalamus, where the HPA axis activation occurs, regulating the stress response [3]. The corticotropin-releasing factor (CRF) regulates HPA axis activation by triggering adrenocorticotropic hormone (ACTH) secretion and consequent cortisol release from adrenal glands, characterizing stress conditions [15].

In this regard, there is extensive literature that aims to understand the close link between depression and stress. Depressed patients present cortisol hypersecretion, dysfunctional glucocorticoid response mechanisms, increased ACTH secretion, inefficient HPA axis suppression in response to exogenous glucocorticoid administration, impaired corticosteroid receptor signaling, and alteration of the levels of CRF [15]. However, contrasting results have been found for CRF [16]. Conflicting data were also described for drugs that act on the HPA axis [17]. Thus, further studies are needed to elucidate the role of the CRF activity on depression, considering the complexity of the pathophysiology of this disorder.

In addition to these factors, several studies confirm the involvement of positive regulation of inflammation in major depression, including in experimental results [18]. According to Gimeno and coworkers (2009) [19], depression occurs before inflammation, rather than as a result of it. However, depressed patients show all chemical signs of the inflammatory response, such as the increased concentration of acute phase mediators and expression of proinflammatory cytokines and their receptors, and high levels of chemokines and adhesion molecules found in blood-cerebrospinal fluid (CSF) [3]. Thus, anti-inflammatory therapy becomes a potential treatment, since the correlation between the pathogenesis of depression and immune activation and cytokine secretion, such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), interferon-γ (IFN-γ), leukotrienes (LTs) and prostaglandins (PGs) have been demonstrated [18, 20]. This robust finding indicates IL-6 and TNF-α as the most frequent cytokines involved in the pathogenesis of depression. Furthermore, antibodies targeting IL-6, interleukin-12/23, and TNF-α displayed a positive impact on the main depressive symptoms [21].

Exacerbated central activation of the inflammatory response may interfere with several known processes in the pathophysiology of depression, including neurotrophic support, oxidative stress, neurogenesis, and apoptosis [22, 23]. Thus, the scientific literature has reported the antidepressant efficacy of anti-inflammatory drugs [20]. However, the use of the anti-inflammatory therapeutic strategy in the clinical practice of primary depressive disorder patients is still incipient, despite the positive effects found in experimental studies. Thus, the most effective mechanism of anti-inflammatory action for the treatment of depression must be well outlined to expand the arsenal of antidepressant therapy, especially for patient's refractory to conventional treatment.

The involvement of oxidative stress in depressive disorders has also been the focus of studies, highlighting that oxidative unbalance plays a pivotal role in the etiology of the disease. Depression has been related to increased free radical production and low antioxidant concentration [24]. Some studies have shown that extracellular antioxidant chemical compounds are affected by depression. Depressed patients present reduced serum levels of vitamin E, uric acid, albumin, and glutathione. In addition to the non-

Table 1. Pathophysiological factors of depression.

Pathophysiological Theory	Relevant Features
Monoaminergic neurotransmitters	Decreased levels of serotonin, norepinephrine, and dopamine
HPA axis	Cortisol hypersecretion, dysfunctional glucocorticoid response mechanisms, increased ACTH secretion, and alteration of the CRF levels
Inflammatory process	Increased levels of IL-1, IL-6, TNF-α, IFN-γ, LTs, and PGs
Oxidative stress	Reduced levels of vitamin E, uric acid, albumin, glutathione, and altered levels of catalase and superoxide dismutase
Neurotrophic factors	Deficiency of neurotrophic factors, such as BDNF and neurotrophin-3

enzymatic antioxidants, enzymatic antioxidants are also essential for maintaining oxidative balance, in which catalase and superoxide dismutase activity appear to be altered by depression disorder [24].

Furthermore, the BDNF supports the neurotrophic hypothesis of depression. The relationship between neuroplasticity and stress stimuli has been explored. Stress conditions can lead to changes in neural processes and the number of neurons [10]. In neuroimaging studies with depressive patients, selective structural changes in different limbic and non-limbic brain regions, such as the prefrontal and cingulate cortex, were identified [25, 26]. Impairment of structural plasticity and cellular resilience may be closely related to depressive disorders, with deficiency of neurotrophic factors, such as BDNF and neurotrophin-3 [26, 27]. The reduction of BDNF compromises synaptic transmission on mood--controlling structures, such as the hippocampus and prefrontal cortex, and decreases neurogenesis [28-30]. According to experimental studies of depressive episodes, BDNF is directly related to stress, neurogenesis, and hippocampal atrophy [3]. Therefore, it should be noted that the increase of monoamine concentrations in the synaptic cleft by antidepressant treatments currently used in clinical practice stimulates, through adaptive mechanisms, the positive regulation of BDNF [28-30]. For example, agomelatine and vortioxetine treatments increased BDNF levels in patients affected by depressive disorders [31, 32]. Thereby, BDNF is closely linked to the other factors related to depression, according to the monoaminergic and inflammatory process theory [3]. The pathophysiological factors of depression are summarized in Table **1**.

4. LINALOOL AS A THERAPEUTIC TOOL IN DEPRESSION

The potential activity of linalool in the CNS has been investigated for some time, and studies on its mechanism of antidepressant action have become of greater interest in recent years. Thus, new studies have been stimulated to expand knowledge about the interaction of linalool with the targets of monoaminergic pathways, using other types of antagonists and different pathways, in addition to treatments and behavioral models, including their kinetics. Although still scarce, existing research points to linalool as a promising natural compound in treating depression due to its interaction with the monoaminergic system's different targets and classic antidepressant drugs (Fig. **1**).

4.1. Linalool Action on the Pathophysiological Factors of Depression

Our research group has studied linalool as an antidepressant agent since 2016. The potential for interaction of linalool with the CNS is significant, allowing it to be a new source of natural compounds capable of intervening in the pathways of neurodegenerative and behavioral disorders, including depression. In a work entitled "Linalool-rich essential oils from the Amazon display antidepressant-type effect in rodents," some aromatic plants' essential oils from Brazilian Amazon, rich in linalool, showed antidepressant activity on mice behavioral models [33]. Our study suggested the interaction of linalool with one or more pathophysiological factors of depression.

4.2. Linalool Action in Monoaminergic System

Studies of the potential involvement of the mechanism of action of linalool on the pathways of the monoaminergic system in antidepressant activity are still scarce. The first evidence emerges from the study by Guzmán-Gutiérrez and co-workers (2012) [34], showing the antidepressant activity of the essential oil and main constituents of *Litsea glaucescens* Kunth, as linalool and β-pinene, on the forced swimming model in mice. The antidepressant-like activity of linalool was subsequently ratified through the same behavioral model [9]. Additionally, the study evaluated the antidepressant mechanism of action of linalool using serotonergic, dopaminergic, and noradrenergic receptor antagonist drugs. The results suggest that prior administration of a serotonergic receptor antagonist (5-HT_{1A}) blocks the antidepressant activity of linalool. However, using a serotonin synthesis inhibitor did not reverse this activity, suggesting the interaction of linalool with postsynaptic 5-HT_{1A} receptors. In addition to these receptors, pretreatment with an α_2 adrenergic receptor antagonist also reversed the effect of linalool. Therefore, the study suggests that the mechanism of linalool antidepressant action is due to its interaction with the serotoninergic and noradrenergic pathways [9].

In another study, lavender (*Lavandula angustifolia* Mill.) essential oil and linalool, its primary constituent, were evaluated for pharmacological targets involved in antidepressant effects. The results showed that both lavender oil and linalool inhibit serotonin reuptake. These findings may explain the antidepressant pharmacological activity shared by Lavender essential oil and linalool [35]. In a later

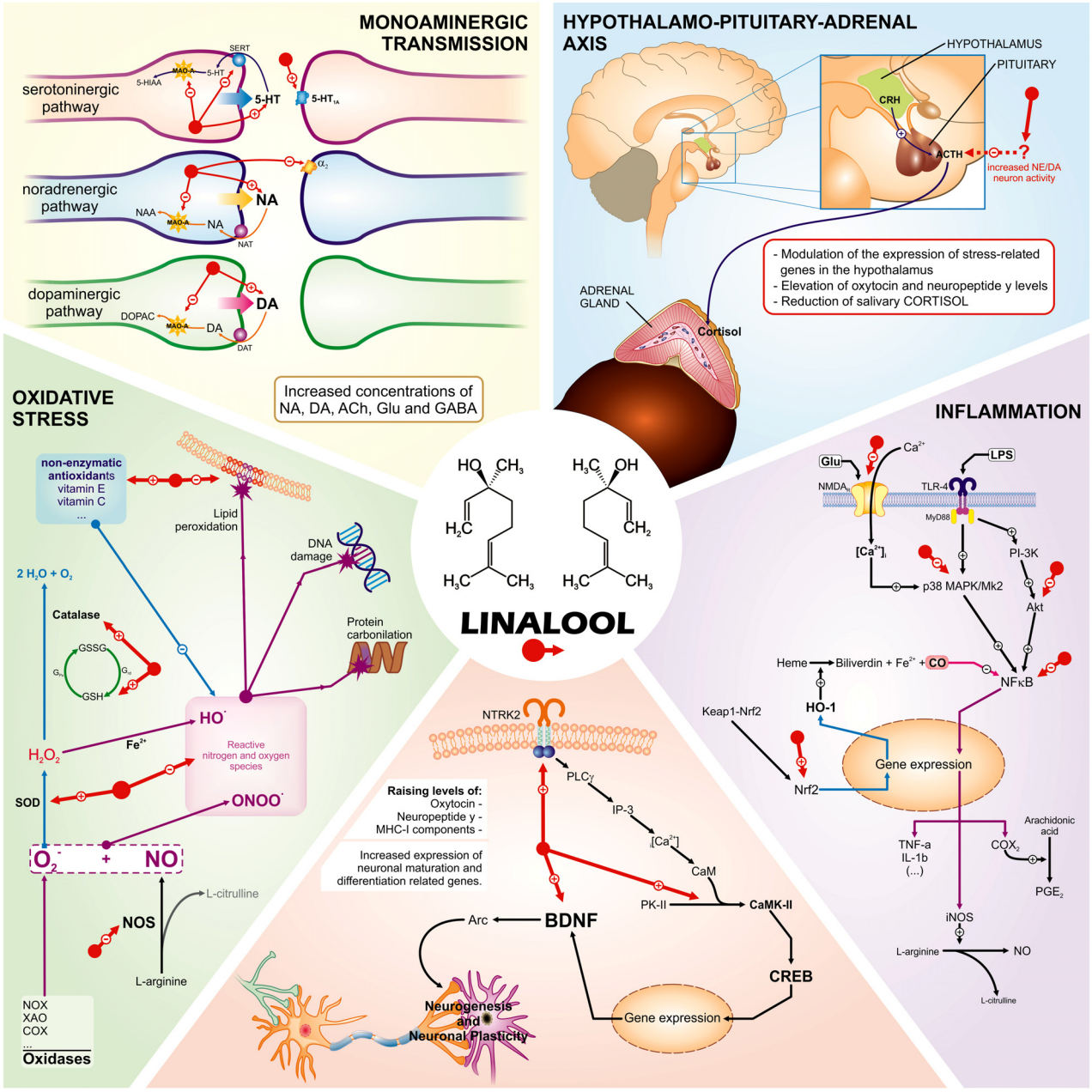

Fig. (1). Hypothetical representation of potential linalool interaction targets on several pathophysiological factors of depressive disorders.
Abbreviations: 5-HT_{1A}: serotonergic receptor, α_2: noragrenergic receptor, α_1: noragrenergic receptor, ABTS: 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), ACTH: adrenocorticotropic hormone, AKT: protein kinase B, ASC: apoptosis-associated speck-like protein containing a caspase-recruitment domain, BDNF: brain-derived neurotrophic factor, BrdU: bromodeoxyuridine, CALNN: Cys-Ala-Leu-Asn-Asn, CaMKII: calcium-calmodulin-dependent protein kinase II, cAMP: cyclic adenosine monophosphate, CNS: Central Nervous System, COX-2: cyclooxygenase 2, CRF: corticotropin-releasing factor, CSF: cerebrospinal fluid, DNA: deoxyribonucleic acid, HO-1: heme oxygenase-1, HPA: Hypothalamic-Pituitary-Adrenal, IFN-γ: interferon-γ, IL-1: interleukin-1, IL-1α: interleukin-1α, IL-1β: interleukin-1β, IL-6: interleukin-6, iNOS: inducible nitric oxide synthase, LPS: lipopolysaccharides, LTs: leukotrienes, MAPK: mitogen-activated protein kinase, NF-κB: nuclear factor kappa B, NLRP3: Nod-like receptor family, pyrin domain containing 3, NMDA: N-methyl-d-aspartate, NO: nitric oxide, Nos2: nitric oxide synthase 2, Nrf2: nuclear factor erythroid-2-related factor 2, PGE2: prostaglandins E2, PGs: prostaglandins, TLR4: toll--like receptor 4, TNF-α: tumor necrosis factor α, TrkB: tropomyosin receptor kinase B, UVB: ultraviolet –B. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

investigation, the anti-stress effect of linalool was evaluated in mice subjected to sleep deprivation. Treatment with linalool decreased the animals' immobility time in the forced swim test and increased serotonin levels in the hippocampus. Also, linalool attenuated the reduction in sleep deprivation-induced plasma serotonin levels. Thus, the study suggests that linalool positively affects behavioral changes and memory consolidation through modulation of the serotonergic pathway [36]. These studies reveal the possibility of linalool interacting with different targets of the monoaminergic system.

Postsynaptic 5-HT_{1A} receptors' involvement with the antidepressant activity has also been demonstrated by using a serotonergic agonist of this receptor subtype [37]. Besides, there was progressive sensitization of dorsal hippocampal postsynaptic 5-HT_{1A} receptors following chronic use of a tricyclic antidepressant [38]. The scientific literature also describes the interaction of noradrenergic receptors (α1 and α2) with antidepressant drugs [39].

In another study, clonidine, a high-affinity α_2-adrenergic agonist, had similar effects to antidepressants in the forced swimming test in mice [40]. On the other hand, these effects of clonidine were reversed by yohimbine, an α_2 receptor antagonist, which may have occurred in postsynaptic noradrenergic receptors. According to the same study, increased stimulation of postsynaptic noradrenergic receptors relieves depressive symptoms [41]. Also, these findings corroborate the results demonstrated by Guzmán-Gutiérrez *et al*. [9].

Essential oils composed of primary alcohols and monoterpene hydrocarbons, belonging to the same plant biosynthetic pathways of linalool, also showed antidepressant activity by monoaminergic modulation, primarily of the serotoninergic pathway, through interaction with the 5-HT_{1A} receptor [42-44]. Together, these findings indicate the need for further investigation on the mechanism of antidepressant action of linalool and similar compounds, particularly on the monoaminergic hypothesis of depression.

4.3. Linalool Action on Stress, HPA Axis Modulation, and the Neuroendocrine System

The interaction of linalool with monoamines and HPA axis modulation during stress induction was the study's objective in experimental models. In one of these studies, inhalation of linalool by menopausal rats restored noradrenaline and dopamine levels, which are reduced after stress induction due to high CNS catecholamine turnover [45]. According to study data, inhalation of linalool increased catecholamine levels to the standard index. Thus, the data suggest that linalool inhibits the accelerated turnover of catecholamine metabolism, increasing the activity of adrenergic/dopaminergic neurons, indirectly inducing the concomitant reduction of ACTH in animals. Despite controversial evidence, some studies indicate the potential inhibitory effect of catecholamines on the HPA axis through the regulation of ACTH secretion [46].

Another linalool interaction pathway has also been proposed by Yamamoto and co-workers (2013) [47] in which (+)-linalool modulates the genic expression on the hypothalamus in stressed rats, reflecting one of the mechanisms for reducing cortisol during stress. The gene expression profile revealed that treatment with (+)-linalool significantly modified 316 genes related to cell-to-cell signaling and nervous system development in the restrained rats. However, the authors failed to demonstrate the differences in ACTH, corticosterone, and leukocyte concentrations. Later, in a similar study, linalool exposure altered the expression of genes on the hypothalamic region related to synaptic transmission [48]. A comparative analysis of transcription levels demonstrated that the expression of 560 stress-induced probe sets was restored to a normal state. The neurotransmitters involved include oxytocin and neuropeptide Y, downregulated by stress and upregulated after linalool inhalation. Primary histocompatibility complex class I molecules, which are critical to neural development and plasticity, were also involved in altering the gene expression of the hypothalamus. Moreover, linalool restored dopamine, acetylcholine, and glutamate levels, as well as GABAergic transmission.

Investigation of the effects of (-)-linalool inhalation on stress hormones, blood cells, and gene expression has also been performed in rats subjected to a combination of physical and psychological stressors. Genetic ontology analysis revealed that stress-induced gene changes were suppressed by (-)-linalool. The treatment prevented alterations in 109 genes, although increased changes in 6 genes were detected in DNA microarray analysis. Besides, the suppression of changes in blood cell profiles has also occurred. A strong relationship was observed between the (-)-linalool-caused modulation of gene and immune system cell distributions. However, the treatment did not suppress plasma ACTH and corticosterone levels [49]. Probably, this occurred because chirality influences the effects of linalool on the physiological parameters of stress [50]. In another study, lavender essential oil and linalool increased social interaction behaviors and reversed the social aversion of stressed animals, similarly to antidepressant agents [51]. These data suggest that linalool may interact with different targets to modulate the HPA axis.

Evidence of linalool's influence on stress modulation in humans was also reported in a 24 volunteers' study of an experimental stress model, where linalool inhalation modulated stress response through changes in physiological parameters, such as reduced blood pressure levels, heart rate variation, and salivary cortisol [50]. In a similar study, inhalation of linalool-rich lavender essential oil also reduced cortisol levels and daytime blood pressure in 83 stressed prehypertensive subjects [52]. Also, lavender oil reduced cortisol and relieved stress symptoms in students who performed arithmetic tasks, such as a mental stressor [53] and stressed women suffering from urinary incontinence [54]. Cortisol reduction was also detected in healthy volunteers' saliva after lavender oil inhalation [55].

In a recent study, linalool-rich lavender essential oil showed a positive effect on depressive-type behaviors, in-

creased neurogenesis, and dendritic complexity of rats in a model of depression, anxiety, and reduced neurogenesis induced by chronic corticosterone administration [56]. The study revealed that lavender essential oil reversed corticosterone-induced weight loss of the adrenal gland and normalized serum hormone levels 2-3 days after the treatment. Therefore, essential oil improved negative HPA axis feedback caused by exogenous corticosterone administration. In addition, lavender essential oil also upregulated the BDNF index and increased peripheral oxytocin levels, which had a protective effect against dorsal hippocampal stress damage [56, 57].

In a previous study, essential oil inhalation of the basil (*Ocimum basilicum* L.), which presents linalool as the main constituent, showed antidepressant effect by positive modulation of glucocorticoid receptor and BDNF gene, mRNA, and protein expressions in an equal manner than the standard drug fluoxetine. Also, the oil reduced the serum corticosterone levels and the hippocampal nerve cell atrophy, restoring the number of astrocytes and hippocampal nerve and normalizing glial apoptotic cells in stressed animals [58].

The linalool action on the HPA axis is still not very well understood. In animal studies, conflicting evidence of linalool activity on ACTH and corticosterone concentrations has been presented, while in humans, robust evidence points to its action in reducing cortisol levels. However, in preclinical studies, linalool under stressful conditions had effects on stress-related biological responses through modulation of the expression of hypothalamic genes [45, 47, 50].

Morphofunctional changes in CNS caused by dysregulation of the HPA axis are closely associated with the onset of depressive symptoms [15]. In experimental models, linalool prevented or restored stress-induced genes changes related to neural development, plasticity, and synaptic transmission [47, 48]. It is also possible that other mechanisms would be involved, such as the interaction with catecholamines and BDNF. Thus, linalool becomes promising for the treatment of various diseases that are related to HPA axis dysregulation. Currently, linalool is used mainly in aromatherapy, producing beneficial effects for treating depression, anxiety, and stress [4, 7].

4.4. Linalool Action on the Inflammatory Process

The anti-inflammatory activity of linalool is already well established. Several studies describe such activity through *in vitro* and *in vivo* models. In experimental models of inflammation, one of the enantiomers, the racemic mixture or undetermined enantiomers, inhibits the inflammatory response and reverses the main signs of inflammation [59]. CNS studies have demonstrated the importance of cytokines role, such as TNF-α, interleukin-1β (IL-1β), interleukin-1α (IL-1α), IFN-γ, in the inflammatory process [60]. According to this study, (-)-linalool inhibited the behavioral nociceptive responses of mice in a model of inflammatory hypersensitivity induced by IL-1β and TNF-α, blocking N-methyl-d-aspartate (NMDA) receptors.

In a recent study, the expression of IL-1β, nitric oxide synthase 2 (NOS2), TNF-α, and cyclooxygenase 2 (COX-2) genes were evaluated to determine whether they were involved in the linalool protective effect after NMDA induced excitotoxicity in the mice hippocampus. The results suggest that NMDA increased COX-2 gene expression while linalool treatment reversed the elevation of this inflammatory mediator. Linalool reduced NOS2 gene levels, while the results showed no efficiency to IL-1β and TNF-α [61]. In a model of inflammation induced by lipopolysaccharides (LPS), linalool inhibited the synthesis of TNF-α, IL-1β, nitric oxide (NO), and prostaglandins E2 (PGE2) through the activation of the nuclear factor erythroid-2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signaling pathway. Also, LPS-induced nuclear factor kappa B (NF-κB) activation was inhibited by linalool in a dose-dependent manner [62]. Lately, daily use of intranasal linalool has produced an anti-inflammatory effect through the reduction of IL-1β and COX-2 levels *in vivo* and *in vitro* excitotoxicity models. It has also shown microglial protective activity in supporting neurological and cognitive recovery after an ischemia process [63].

Similarly, linalool reversed the neuropathological and behavioral deficiencies in a model of Alzheimer's disease in mice through an anti-inflammatory effect [64]. According to the results, linalool treatment reduced the inflammatory markers up-regulated in animals affected by Alzheimer's disease, such as IL-1β, p38 mitogen-activated protein kinase (MAPK), COX-2, and inducible nitric oxide synthase (i-NOS). Besides, (-)-linalool prevented and recovered the inflammatory response of astrocytes induced by the combination of LPS and tryptase in an *in vitro* study [65]. In another inflammatory challenge study, (-)-linalool attenuated the carrageenan-induced inflammatory hyperalgesia and inhibited the development of L-glutamate and PGE2-induced inflammatory hyperalgesia, possibly through central mechanisms [66]. These studies ratify linalool as an anti-inflammatory agent, revealing its action on a wide range of cytokines and inflammatory mediators.

Peripherally, there is also evidence of linalool anti-inflammatory activity. In a recent study, linalool attenuated pulmonary inflammation and exacerbated ovalbumin-induced mucus production, and suppressed the recruitment of inflammatory cells and molecules in mice [67]. Also, linalool blocked primary inflammatory targets related to the inflammatory course, such as protein kinase B (AKT), MAPKs, and NF-κB. Thus, the study suggests that linalool presents an anti-inflammatory protective effect to asthmatic symptoms. In another study, oral administration of linalool prevented endotoxin-induced systemic inflammation by inhibiting NF-κB and suppressing the expression of toll-like receptor 4 (TLR4) pathway signaling molecules. Besides, linalool also suppressed the expression of key molecules of the Nod-like receptor family, pyrin domain containing 3 (NLRP3) signaling pathway such as apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC), NLRP3, and caspase-1 [68].

In addition to its effects on stress conditions, linalool's anti-inflammatory properties have been well documented. The central mechanisms of anti-inflammatory action elicit the linalool as a useful agent in treating depression, also acting on this significant pathophysiological factor.

4.5. Linalool Action on Oxidative Stress

The ability of free radical scavenging is an antioxidant feature that plays a crucial role in reducing cell damage. Linalool has been reported for its antioxidant activity on the oxidative stress related to depression in numerous works of literature, which confers the possible contribution in such pathophysiological factors [24, 69].

Linalool isolated from the essential oil of ginger (*Zingiber officinale* Roscoe) rhizomes showed a significant antioxidant effect, displaying a medium inhibitory effect on erythrocyte hemolysis and a slight inhibitory effect on the 2,2'-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) method [70]. According to this study, ginger oil and linalool can produce natural antioxidants and flavoring agents. In a posterior study, linalool on the surface of modified glutathione gold nanoparticles, or linked to the Cys-Ala-Leu and lipoic acid, displayed a protective effect on oxidative stress induced by hydrogen peroxide in guinea pig brain tissue [71, 72]. The provided neuroprotection was mediated by eliminating peroxyl radicals and increased levels of superoxide dismutase and catalase, reducing oxidative deoxyribonucleic acid (DNA) damage [73]. Also, linalool presented a neuroprotective effect against the acrylamide-induced neurotoxicity model in rats. According to the study, administration of (-)-linalool increased glutathione content in the cerebral cortex, and reduced malondialdehyde concentration, and the abnormalities caused by acrylamide [74]. Such results have been confirmed by other neuronal injury models induced by oxygen and glucose deprivation, in which (-)-linalool showed a neuroprotective effect through the decrease of oxidative stress due to its ability to eliminate free radicals, such as peroxyl radicals, restoring the reduced activities of superoxide dismutase and catalase associated to the minimization of reactive species oxygen [75].

In another study, linalool antioxidant activity has been identified as a potential mechanism of action to attenuate uremia-induced vascular calcification in rats. In the same study, linalool showed moderate superoxide radical scavenging ability and low hydrogen peroxide scavenging ability [76]. Thus, linalool negatively regulated oxidative stress in uremic animals due to its moderate antioxidant action, and this compound directly reduced the synthesis of superoxide radicals. Also, linalool showed a protective effect in oxidative stress conditions by preserving and restoring mitochondrial function [61].

The protective and therapeutic effects of linalool in other body systems were also determined by its antioxidant capacity on doxorubicin-induced cardiotoxicity in rats through histopathological and biochemical methods. Linalool treatment significantly increased glutathione, superoxide dismutase, and catalase levels, relieving the symptoms of doxorubicin-induced cardiomyopathy [77]. Also, linalool prevented the synthesis of reactive oxygen species, depletion of endogenous antioxidant compounds, and lipid peroxidation while eliminated free radicals in human epithelial cells exposed to ultraviolet-B (UVB) [78]. Additionally, inhalation of linalool increased the antioxidant activity in patients with carpal tunnel syndrome [79]. In a *Pasteurella multocida*-induced lung inflammation, linalool showed a protective effect by oxidative stress modulatory activity [80]. According to the results, linalool increased superoxide dismutase activity, reduced the accumulation of reactive oxygen species, and increased Nrf2 expression. Thus, an alternative mechanism of modulation of linalool antioxidant activity would be activating the Nrf2 signaling pathway. Subsequently, coriander (*Coriandrum sativum* L.) oil and linalool displayed antioxidant activity by eliminating free radicals and significantly inhibiting lipid peroxidation [81, 82]. These varieties of results suggest different mechanisms for linalool antioxidant action, focused on enzymatic antioxidant modulation, as well as free radicals scavenging activities.

In an innovative study, a simple, fast, and inexpensive method was proposed to determine and compare the antioxidant activity of different monoterpenes. Monoterpenes' ability to prevent oxidation of a dye in the presence of a strong oxidant was evaluated. The results suggest an intense antioxidant activity of linalool in a lower concentration than the other monoterpenes [83]. In another study, linalool showed antioxidant activity by its co-oxidation with cumene, used as a reaction substrate [84].

Although the involvement of oxidative stress with depression is not well elucidated, studies have correlated such a possible relationship. Thus, a significant antioxidant activity of linalool already described in several studies may act synergistically with its effects on the other pathophysiological factors of the disease, converging to general antidepressant activity. It is also important to note that linalool antioxidant activity can eliminate free radicals and elevate antioxidant levels.

4.6. Linalool Action in BDNF and Neurotrophic Theory of Depression

In general, the potential interaction of linalool with neurotrophic factors, especially BDNF and neuroplasticity, still has little evidence. However, recent studies have reported a close relationship. In a model of Alzheimer's disease in mice, the lavender oil and linalool improved animals' cognitive function through various mechanisms, highlighting the neuroprotective effect against oxidative stress. The treatment restored the reduced expression of synaptic plasticity-related proteins, such as calcium-calmodulin-dependent protein kinase II (CaMKII), BDNF, and tropomyosin receptor kinase B (TrkB), in the hippocampus [85].

In another study, gene expression in the hypothalamus of rats exposed to linalool after restriction stress induction was evaluated by analyzing genetic ontology. Findings revealed that linalool inhalation regulated the expression of genes related exclusively to synaptic transmission, nerve impulse transmission, and the peptide antigens' processing and presentation [48]. Thus, linalool restored expression of genes encoding neurotransmitters, such as oxytocin and neuropeptide Y, and primary histocompatibility complex class I molecules. Therefore, linalool promoted positive effects on synaptic connectivity, development, and neuronal plasticity.

According to Leuner and co-workers (2012) [57], oxytocin improves plasticity, increases cell proliferation and hippocampal neurogenesis.

In a similar study, inhalation of (-)-linalool increased the expression of genes related to neuron differentiation, associated with the increase of genes expression related to neurite development, and transcriptional regulatory factors, which are fundamental for neuronal maturation [86]. This study showed that (-)-linalool positively affects neuron maturation by regulating neuronal connectivity and synaptic formation in the hypothalamus. These findings suggest different mechanisms of action of linalool on neuroplasticity.

In addition to linalool isolated studies, linalool-rich essential oils works have also been performed. In one of these studies, inhaling linalool-rich lavender essential oil increased the number of positive bromodeoxyuridine (BrdU) cells (neuronal cell proliferation marker) in the hippocampus and subventricular zone, as reversed corticosterone-induced suppression of neurogenesis in rats. The improvement in hippocampus dendritic complexity and increase of immature cells in the subventricular zone were also found. Besides, there was an increased concentration of BDNF and oxytocin. Thus, the study suggests the positive effect of linalool-rich lavender essential oil on depressive-like behaviors, neurogenesis, and dendritic complexity [56].

The attenuating effect of inhaling the basil essential oil, which has linalool as its primary constituent, was evaluated for changes associated with unpredictable moderate stress through an animal model of depression [58]. According to the study, the basil essential oil reduced hippocampal nerve cell atrophy and restored the reduced number of stress-induced astrocytes. In addition, the essential oil reduced nerve and glial apoptotic cells in the hippocampus of stressed animals. The authors postulated that the linalool antidepressant mechanism of action relies on the positive modulation of gene and protein expression of BDNF and glucocorticoid receptors [58].

The development of studies on neuroplasticity has identified its involvement with significant depression. Besides, it has identified the positive activity of traditional antidepressants on this etiological factor [3]. Additionally, clinically practiced drugs have evidenced the interaction of natural compounds on neuroplasticity. Recent investigations indicate the beneficial effects of linalool by increasing neurotrophic factors, especially BDNF, triggering neuronal differentiation and neuroplasticity in limbic regions [85, 86]. Besides, linalool's regulatory action on the HPA axis would be one of the consequences of this mechanism. All pathophysiological factors of depression are closely related. Thus, linalool could interact directly with such factors by different mechanisms of action or act on a specific pathway, which may display a cascade of indirect effects on the other depressant molecular mechanisms. Only through advanced new studies, these questions will be answered.

4.7. New Approaches on the Pathogenesis of Depression

4.7.1. Linalool Versus the Microbiota-gut-brain Axis

In recent years, significant progress on the knowledge of bidirectional communication between the CNS and the gastrointestinal tract has been postulated. Several pieces of evidence have also emerged revealing the role of the gut microbiota on the gut-brain relationship [87, 88]. The hypothesis of the microbiota-gut-brain axis imbalance has been linked to the pathogenesis of depression [89]. Alterations in gut microbiota can lead to several conditions, such as increased gut barrier permeability, modulation of release and efficacy of monoamines, alteration of the HPA axis activity, activation of the systemic inflammation and immune response, as well as the BDNF levels modification [90]. Thus, the imbalance of the microbiota-gut-brain axis has been closely associated with several pathophysiological factors of depression.

In this scenario, the linalool antimicrobial activity against pathogens on the digestive system has been a pivotal role related to the potential beneficial effects on the regulation of the gut microbiota, with contributions on the depressive symptoms. Studies revealed that linalool was effective in inhibiting pathogenic strains of *E. coli*, *P. aeruginosa*, *S. typhimurium*, *S. aureus*, *C. botulinum*, *C. perfringens*, *S. enterica*, *B. fragilis*, *S. enteritidis*, *L. monocytogenes*, and *B. thetaiotaomicron* [91-93]. In addition, linalool presented moderate activity against six other harmful intestinal bacteria [94, 95].

Importantly, preclinical evidence of the positive effect of linalool-rich essential oils on gut microflora emphasizes that intestinal pathogen reduction has been associated with the resident microbiota increase or preservation (*i.e.*, *Lactobacillus* spp) [96-99]. An additional mechanism of the regulatory and stabilization of the microbiota may be attributed to the increase of digestive enzymes activity and positive histomorphological changes of the intestinal tissue, such as increase of the villus height and crypt depth, as well as reduction of goblet cells and epithelial thickness [96, 97, 100]. These positive changes in the structure of intestinal mucosa indicate the improvement of intestinal health [100]. *in vitro* assays have reinforced the antibacterial effect against *E. coli* of linalool-rich essential oils, due to which these natural products have been suggested as good candidates for the treatment of irritable bowel syndrome, in which one of the causative factors relies on the alteration of gut microbiota followed by infection [101].

The advancement of research on the dysfunction of the microbiota-gut-brain axis has elicited several pieces of evidence linking the imbalance of gut microbiota on the pathophysiological factors of depression. The linalool may interact with several pathophysiological factors of the disease, as previously discussed. In addition, studies have shown the positive impact of linalool and linalool-rich essential oils on the modulation of the gut microbiota, which opens the possibilities to investigate the relationship of the linalool bioactive compound *versus* depression disorder. This finding consists of an additional element that reinforces linalool as a probable new candidate for the treatment of depression.

4.7.2. Linalool Action in the Glutamatergic System

Due to the critical limitations of conventional antidepressants, numerous studies have focused on the glutamatergic system, especially the NMDA receptor, to find therapeutic alternatives for the treatment of depression [102]. Several pieces of evidence support the involvement of glutamate-NMDA receptor overstimulation on the etiopathology of depression through the animal models of depression, postmortem tissues of suicide victims, and detection of changes in NMDA receptor activity after chronic administration of antidepressants [103]. The findings suggest that the blockade of NMDA receptors elicits improvement or remission of symptoms in the depressed state [102].

Recently, considerable advancement in antidepressant therapy has occurred with the approval of esketamine, an NMDA receptor antagonist, to treat resistant depression in adults [102]. However, the approval of this ketamine isomer follows significant restrictions due to adverse effects. Dissociation and delirium may occur in low doses shortly after the start of the infusion, which tends to disappear before the antidepressant response [102]. Our research group has evaluated several intermittent ketamine exposure implications, in which anxiogenic- and depressive-type behaviors, as well as memory impairment related to hippocampal and systemic oxidative damage, were found in female adolescent rats [104].

Despite dual evidence and a still poorly understood mechanism, the potential antidepressant activity of NMDA receptor blocker compounds highlights a possible new target for linalool's antidepressant effect. The properties of linalool as an antagonist of NMDA receptors have been proposed through the antinociceptive, analgesic, sedative, and anticonvulsant challenges [5, 105]. Finally, linalool showed anxiolytic and antidepressant effects by NMDA receptor blockade and inhibiting the reuptake of serotonin [35].

These findings on the glutamatergic system modulatory effects reflect an additional target for the linalool antidepressant action. However, the antidepressant effect cannot be explained exclusively by the interaction with NMDA receptors. We suggest that the pleiotropic property of linalool confers the antidepressant response due to direct mechanisms, such as the involvement of several neurotransmitters, and indirect mechanisms, such as adaptive responses.

4.8. Other Biological Activities of Linalool

In addition to the action on the pathophysiological factors of depression, linalool has several other biological activities well documented in the scientific literature. In one of these studies, anticonvulsant activity of enantiomers and the racemic mixture of linalool was demonstrated through the pentylenetetrazole- and picrotoxin-induced challenge in mice [106]. Previously, linalool also showed anticonvulsant activity in glutamate-related seizure models [107]. According to Brum *et al*., the direct interaction with NMDA receptors consists of the mechanism of anticonvulsant action elicited by linalool [108]. In another investigation, linalool-rich rosewood (*Aniba rosaeodora* Ducke) oil, (-)-linalool, and its racemate inhibited the activity of adenylate cyclase in the retina of chicks, preventing cell accumulation of cyclic adenosine monophosphate (cAMP), which has been implicated in the pathophysiology of epilepsy. Thus, the study suggests that the enzyme's inhibition would be a secondary mechanism to these constituents' relaxing and anticonvulsant action [109]. Vago-vagal bradycardia and depressor reflex induced by linalool-rich rosewood oil have also been reported in rats [110].

Sedation is another well-established biological activity of linalool. In a mice model, inhaled linalool produced sedative effects, eliciting hypothermia, reducing locomotion, and increasing the sleep time induced by pentobarbital [111]. The essential oil of *Litsea glaucescens* Kunth, constituted by linalool and β-pinene as active principles, was administered intraperitoneally in mice, exhibiting sedative effects without affecting muscle strength and motor coordination of the animals [34]. In another experimental protocol, coriander (*Coriandrum sativum* L.) seed oil and linalool showed similar sedative effects after intracerebroventricular administration in neonatal chicks [112]. The linalool-rich rosewood (*Aniba rosaeodora* Ducke) essential oil also elicited a sedative effect and depressed the excitability of the sciatic nerve of mice [113].

Addressing other activities of linalool on the CNS, there are pieces of evidence of its potential anxiolytic action. In a recent study, linalool inhalation induced a significant anxiolytic-type effect in mice classic behavioral tests. There was no effect in anosmic mice, indicating that it occurs through the olfactory input of linalool. The anxiolytic-type effects of linalool were antagonized by flumazenil, demonstrating the interaction with GABAergic transmission [114]. Another work revealed that lavender (*Lavandula angustifolia* Mill.) essential oil and linalool neutralized the social defeat-induced social aversion in mice tests, promoting sedative effects. Thus, according to the authors, both oil and linalool *per se* may be a valuable tool to treat anxiety and social disorders caused by social stress [51]. Linalool inhalation displayed a mice anxiolytic-type activity, increasing social interaction and decreasing the animals' aggressive behavior. The study suggested that intranasal administration of linalool-rich essential oils promotes relaxation and anxiolytic activity [115]. A variety of experimental studies have revealed anxiolytic-type effects derived from linalool-rich essential oils (*i.e.*, *Cinnamomum osmophloeum* Kaneh.), linalool enantiomers (*i.e.*, (+)-linalool), and linalool racemic mixture. The results showed a reduction in serotonin, dopamine, and norepinephrine released by the frontal cortex and hippocampus, while there was also an increase of dopamine in the mice striatum [116]. All the studies mentioned above reveal the broad spectrum of a promising bioactive chemical compound and biological activities of linalool on the CNS and improve its importance as a potential therapeutic tool for neurological and psychiatry disorders. Table **2** describes the experimental model, extract, dose, and treatment of the literature related to the linalool activities on the pathophysiological factors of depression and other activities on the CNS.

Table 2. Summary of studies of the linalool action on the pathophysiological factors of depression and other activities on the central nervous system.

Linalool Action on Monoaminergic System				
References	**Experimental Model**	**Extract/Constituent**	**Concentration/Dose**	**Duration of Treatment**
Guzman-Gutierrez *et al*., 2015	Pre-treatment *in vivo*	β-pinene and linalool	β-pinene *i.p.* and linalool *i.p.* (100 mg/kg)	3 times (24, 18 and 1 h before forced swimming test)
Guzman-Gutierrez *et al*., 2012	Pre-treatment *in vivo*	*Litsea glaucescens* essential oil (linalool 3.64%), β-pinene and linalool	*Litsea glaucescens* essential oil i.p. (100 and 300 mg/kg), β-pinene i.p. and linalool i.p. (100 mg/kg)	3 times (24, 18 and 1 h before behavioral tests)
López *et al*., 2017	Pre-, co-treatment *in vitro*	Lavender essential oil (linalool 37.4%), linalool and linalyl acetate	Lavender oil (0.8, 4 and 8 µl/ml) and linalool (8, 0.8, 0.08 and 0.008 µl/ml); lavender oil – cell viability (0.05, 0.1, 0.5 and 1 µl/ml)	Incubation for 30 min (MAO-A); 2 h (SERT); 40 min ($GABA_A$); 1 h (NMDA receptor); 0, 2 and 24 h before hydrogen peroxide, malonate and $A\beta_{25-35}$
Lee *et al*., 2018	Post-treatment *in vivo*	Linalool	Linalool i.p. (0.3, 1 and 3 mg/kg)	24 h after sleep deprivation model
Linalool Action on Stress, HPA Axis Modulation, and Neuroendocrine System				
References	**Experimental Model**	**Extract/Constituent**	**Concentration/Dose**	**Duration of Treatment**
Yamada *et al*., 2005	Pre-, post-treatment *in vivo*	Lavender essential oil and linalool	Inhalation of lavender oil and linalool – 0.3 and 0.7 ml in a plastic cage (32 cm × 21 cm × 13 cm)	Twice a day/3 days one month after ovariectomy and before inhalation ether vapor
Yamamoto *et al*., 2013	Co-treatment *in vivo*	(+)-linalool	Inhalation of (+)-linalool – 20 µl in a 40 l box	During restraint stress
Yoshida *et al*., 2017	Co-treatment *in vivo*	Linalool	Inhalation of linalool – 20 µl in a 40 l box	During restraint stress
Nakamura *et al*., 2009	Co-treatment *in vivo*	(-)-linalool	Inhalation of (-)-linalool – 20 µl in a 40 l box	During restraint stress
Höferl *et al*., 2006	Co-treatment *in vivo*	(-)-linalool and (+)-linalool	Inhalation of (-)-linalool (2.7 mg/m^3) and (+)-linalool (9.8 mg/m^3)	During standardised stress task
Caputo *et al*., 2018	Pre-, post-treatment *in vivo*/co-treatment *in vitro*	Lavender essential oil (linalool 33.1%) and linalool	Lavender oil i.p. (200 mg/kg) and linalool i.p. (100 mg/kg)/lavender oil (100-400 µg/ml) and linalool (100-200 µg/ml)	30 min before experiment 1; 10 min after stress and 30 min before experiment 2; 17 days after acute or a chronic administration (once a day/10 days), 30 min before stress and 1 h 10 min before behavioral tests/cells were treated for 24 h
Kim *et al*., 2012	Post-treatment *in vivo*	Essential oils mixed – lavender, ylang-ylang, marjoram and neroli	Inhalation of lavender, ylang-ylang, marjoram and neroli oils – the oils were blended at a 20:15:10:2 ratio	Immediate effects (2 min); four weeks (24 h)
Toda and Morimoto, 2008	Post-treatment *in vivo*	Lavender essential oil	Inhalation of lavender oil – 150 µl infiltrated into filter paper to 10 cm from the nose	After the arithmetic task
Seol *et al*., 2013	Co-treatment *in vivo*	Lavender (linalool 33.3%) and clary (linalool 17.7%) essential oils	Inhalation of lavender oil (5%); Inhalation of clary oil (5%)	1 single-dose inhalation during urodynamic examination
Atsumi and Tonosaki, 2007	Pre-treatment *in vivo*	Lavender and rosemary essential oils	Inhalation of essential oils – 1000 times dilution (low-concentration solution) and 10 times dilution (high-concentration solution)	Natural breathing for 5 min
Sánchez-Vidaña *et al*., 2019	Co-treatment *in vivo*	Lavender essential oil	Inhalation of lavender oil - cotton impregnated with 1 ml (2.5%) in an acrylic fiber box (42 × 30 × 29 cm)	Exposure of 1 h daily for 14 consecutive days (with corticosterone administration)
Ayuob *et al*., 2017	Co-treatment *in vivo*	Basil essential oil (linalool 35.9%)	Inhalation of basil oil - 1 ml (1, 2.5 and 5%) on cotton inside a odor-isolated chamber (32 × 24 × 32 cm)	Once daily for 15 min in the last 2 weeks of exposure to chronic unpredictable mild stress (4 weeks)

(Table 2) contd….

Linalool Action on the Inflammatory Process				
References	**Experimental Model**	**Extract/Constituent**	**Concentration/Dose**	**Duration of Treatment**
Huo *et al*., 2013	Pre-treatment *in vivo*/*in vitro*	Linalool	Linalool i.p. (25 mg/kg)/linalool (40, 80 and 120 µg/ml)	1 h before LPS-induced acute lung injury/1 h before LPS stimulation
Batista *et al*., 2010	Pre-, post-treatment *in vivo*	(-)-linalool	Acute treatment: (-)-linalool i.p. (50 and 200 mg/kg); chronic treatment: (-)-linalool i.p. (50 mg/kg)	A single injection 30 minutes before the inflammatory induction by cytokines, 24 h after the CFA or 7 days after surgery; twice a day (every 12 h) for a period of 7 days for both methods
Sabogal-Guáqueta *et al*., 2019	Co-treatment *in vitro*	Linalool	Linalool 100 µM	Incubated with glutamate or NMDA
Li *et al*., 2015	Pre-treatment *in vitro*	Linalool	Linalool (25, 50 and 100 µg/ml) or (162, 324, 648 µM)	1 h before LPS treatment
Barrera-Sandoval *et al*., 2019	Post-treatment *in vivo*/*in vitro*	Linalool	Bioavailability study: single-dose of linalool v.o., i.p. and i.n. (25 mg/kg); other tests: linalool i.n. (25 mg/kg)/linalool (100 nM)	Once a day for one month after focal ischemia/cells treated for 24 h after glutamate
Sabogal-Guáqueta *et al*., 2016	Post-treatment *in vivo*	Linalool	Linalool p.o. (25 mg/kg)	Every 48 h for 3 months on aged mice with a triple transgenic model of Alzheimer's disease
Hansson *et al*., 2016	Pre-, co-, post-treatment *in vitro*	Cocktail of naloxone, (-)-linalool and levetiracetam	Naloxone (10^{-12} M), (-)-linalool (10^{-6} M) and levetiracetam (10^{-4} M)	Cocktail for 30 min, then, cocktail and LPS + tryptase for 24 h; LPS + tryptase for 24 h, then, LPS + tryptase and cocktail for an additional 24 h; LPS for 24 h, and then the cocktail 3.5 min before glutamate stimulation
Peana *et al*., 2004	Pre-treatment *in vivo*	(-)-linalool	(-)-linalool s.c. (50, 100, 150 and 200 mg/kg)	30 min before carrageenan, L-glutamate and PGE2
Kim *et al*., 2019	Co-, post-treatment *in vivo*/pre-treatment *in vitro*	Linalool	Linalool p.o. (15 and 30 mg/kg)/ linalool (2.5, 5, 10, 20, 40 and 80 µg/ml)	After ovalbumin and alum, linalool for 5 consecutive days; ovalbumin was also administered in the last 3 days of linalool/1 h before incubation with LPS for 24 h
Lee *et al*., 2018	Pre-treatment *in vivo*	*Cinnamomum osmophloeum* Kanehira essential oil (linalool 40.24%), cinnamaldehyde and linalool	*C. osmophloeum* essential oil p.o. (13 mg/kg), cinnamaldehyde p.o. (0.45 and 0.9 mg/kg) and linalool p.o. (2.6 and 5.2 mg/kg)	Every other day for 2 weeks before endotoxin (24 h after)
Linalool Action on Oxidative Stress				
References	**Experimental Model**	**Extract/Constituent**	**Concentration/Dose**	**Duration of Treatment**
Elgendy and Semeih, 2019	Co-treatment *in vitro*	Linalool	Linalool (1.56, 3.125, 6.25, 12.5, 25, 50 and 100 µg/ml)	-
Jabir *et al*., 2019	Pre-treatment *in vivo*/co-treatment *in vitro*	Linalool, GNPs, Linalool-GNPs and linalool-GNPs-CALNN	All the compounds i.p. (500 µg/kg)/linalool (10 µg/ml), GNPs (10 µg/ml), LIN-GNPs (10 µg/ml - 10µg/ml), LIN-GNPs-CALNN (10 µg/ml - 10 µg/ml - 1 µg/ml)	*in vivo* toxicity: once before monitorization for 4 weeks/antioxidant activity (25 min of incubation); anticancer activity (48 h)
Celik and Ozkaya, 2002	Co-treatment *in vivo*	Linalool, lipoic acid and vitamin E	Lipoic acid i.p. (3 mg/kg), vitamin E i.p. (24 mg/kg) and linalool i.p. (120 mg/kg)	Every other day for 4 weeks during H_2O_2-induced oxidative stress
Thapa *et al*., 2019	Pre-, co-treatment *in vitro*	Linalool, nerolidol, thymol, geraniol, methylisoeugenol and agolin	Nerolidol (62.5 ppm), thymol (12.5 ppm), geraniol (125 ppm), methylisoeugenol (125 ppm), linalool (250 ppm) and Agolin (250 ppm)	Incubation for 1 and 24 h (cytotoxicity); 24 h (genotoxicity); 24 h (genoprotection) before exposition genotoxic agents
Mehri *et al*., 2015	Pre-, co-treatment *in vivo*	(-)-linalool	(-)-linalool i.p. (12.5, 25, 50 and 100 mg/kg)	Simultaneously (all doses), 3 days before (12.5 mg/kg) or 3 days after (12.5 mg/kg) starting acrylamide (daily for 11 days) and continued during treatment

(Table 2) contd….

Park *et al*., 2016	Pre-, co-treatment *in vitro*	(-)-linalool	(-)-linalool (10 μM)	Immediately before the initiation of oxygen-glucose deprivation and maintained throughout oxygen-glucose deprivation/re-oxygenation
Kaur *et al*., 2018	Co-treatment *in vivo*/*in vitro*	Linalool	Linalool p.o. (100 and 150 mg/kg)/linalool (50, 100, 150 and 200 μg/ml)	Daily for 4 weeks with phosphate diet after adenine diet for 4 weeks
Sabogal-Guáqueta *et al*., 2019	Co-treatment *in vitro*	Linalool	Linalool 100 μM	Incubation with glutamate or NMDA
Oner *et al*., 2019	Pre-, post-treatment *in vivo*	Linalool	Linalool i.p. (50 and 100 mg/kg)	Daily for 5 days before and after single dose of doxorubicin (treatments in different groups)
Gunaseelan *et al*., 2017	Pre-treatment *in vitro*	Linalool	Linalool (30 μM)	Incubation for 1 h before exposition of UVB-radiation
Seol *et al*., 2016	Post-treatment *in vivo*	Linalool	Inhalation of linalool (1%) – 0.5 ml placed onto a gauze pad (3 × 2 cm^2)	Gauze pad positioned 5 cm from the nose for 10 min in patients with carpal tunnel syndrome
Wu *et al*., 2014	Post-treatment *in vivo*/co-, post-treatment *in vitro*	Linalool	Linalool s.c. (5, 15 and 25 mg/kg)/ linalool (40, 80 and 120 μg/ml)	2 h after infection and then at 12 h intervals/treatment for 6 h; after cells are challenged by *P. multocida*
Duarte *et al*., 2016	Co-treatment *in vitro*	Coriander essential oil (linalool 64.38%) and linalool	Oil of coriander and linalool (0.1-32 μl/ml)	Incubation for 48 h with the *Campylobacter* strains; 24 h with *Chromobacterium violaceum*; 90 min for the DPPH and 2 h for β-carotene bleaching test
Samojlik *et al*., 2010	Pre-treatment *in vivo*/co-treatment *in vitro*	Essential oil of coriander (linalool 74.6%), caraway and linalool	Oil of coriander p.o. (0.03 g/kg) and oil of caraway p.o. (0.13 g/kg)/ both oils (2.5, 5, 7.5, 10 and 12.5 μl/ml); oil of coriander (12.5, 18.75, 25, 50, 75, 100 and 125 μl/ml); linalool (unreported)	Daily for 5 consecutive days before a single dose of CCl_4
Noacco *et al*., 2018	Co-treatment *in vitro*	linalool, geraniol and 1,8-cineole	Linalool, geraniol and 1,8-cineole (6.48 x 10^{-3}-648 mM)	Incubation in the darkness for 5 min
Baschieri *et al*., 2017	Co-treatment *in vitro*	linalool, (+)-limonene and citral	Linalool (28-2800 mM), (+)-limonene (30-1500 mM) and citral (0.15-90 mM)	-
Linalool Action on BDNF Levels and Neurotrophic Theory of Depression				
References	**Experimental Model**	**Extract/Constituent**	**Concentration/Dose**	**Duration of Treatment**
Xu *et al*., 2017	Co-, post-treatment *in vivo*	Lavender essential oil (linalool 37.96%) and linalool	Lavender oil i.p. and linalool i.p. (50 and 100 mg/kg)	Daily for 4 weeks (with D-galactose and $AlCl_3$) and 9 days
Yoshida *et al*., 2017	Co-treatment *in vivo*	Linalool	Inhalation of linalool – 20 μl in a 40 l box	During restraint stress
Nakamura *et al*., 2010	Co-treatment *in vivo*	(-)-linalool	Inhalation of (-)-linalool – 20 μl in a 40 l box	During restraint stress
Sánchez-Vidaña *et al*., 2019	Co-treatment *in vivo*	Lavender essential oil	Inhalation of lavender oil - cotton impregnated with 1 ml (2.5%) in an acrylic fiber box (42 × 30 × 29 cm)	Exposure of 1 h daily for 14 consecutive days (with corticosterone administration)
Ayuob *et al*., 2017	Co-treatment *in vivo*	Basil essential oil (linalool 35.9%)	Inhalation of basil oil - 1 ml (1, 2.5 and 5%) on cotton inside a odor-isolated chamber (32 × 24 × 32 cm)	Once daily for 15 min in the last 2 weeks of exposure to chronic unpredictable mild stress (4 weeks)
Other Biological Activities of Linalool on the Central Nervous System- Anticonvulsant Activity				
References	**Experimental Model**	**Extract/Constituent**	**Concentration/Dose**	**Duration of Treatment**
Sousa *et al*., 2010	Pre-treatment *in vivo*	(-)-linalool, (+)-linalool and racemate of linalool	(-)-linalool i.p., (+)-linalool i.p. and linalool i.p. (100, 200 and 300 mg/kg)	30 min before administration of pentylenetetrazol, picrotoxin and electroconvulsive shock

(Table 2) contd….

Elisabetsky *et al*., 1999	Pre-, co-treatment *in vivo*/co-treatment *in vitro*	Linalool	Linalool i.p. (350 mg/kg); linalool i.c.v. infusion (15, 30, and 45 mM); linalool p.o. (2.2 and 2.5g/kg)/linalool (0.1, 0.3, 1, 3 and 5 mM).	30 min before NMDA; 5 min before quinolinic acid; treatments repeated once every 3 days (6 treatments) – linalool 30 min before pentylenetetrazol/incubation for 15 min with glutamate
Brum *et al*., 2001	Co-treatment *in vitro*	Linalool	Linalool (0.1, 0.3, 1, 3 and 5 mM)	Incubation for 1 h with glutamate, glycine and NMDA antagonist; 30 min with $GABA_A$ agonist
Sampaio *et al*., 2012	Pre-, co-treatment *in vitro*	Rosewood essential oil (linalool 84.8%), (-)-linalool and racemate of linalool	Rosewood oil, (-)-linalool and linalool (40 μM-17.5 mM)	Incubation for 10 min before and additional 20 min with forskolin
Siqueira *et al*., 2014	Pre-, post-treatment *in vivo*/co-treatment *in vitro*	Rosewood essential oil (linalool 87.7%)	Rosewood oil i.v. (1, 5, 10 and 20 mg/kg)/rosewood oil (0.15-771.25 μg/ml)	Before bivagotomy and capsaicin; after capsazepine, ondansetron and HC030031
Other Biological Activities of Linalool on Central Nervous System- Sedative Activity				
References	**Experimental Model**	**Extract/Constituent**	**Concentration/Dose**	**Duration of Treatment**
Linck *et al*., 2009	Pre-treatment *in vivo*	Linalool	Inhalation of linalool (1% and 3%) – sealed cylindrical (internal diameter 15 cm) glass chamber	1 h of inhalation before the evaluation of pentobarbital-induced sleep time and other tests
Guzman-Gutierrez *et al*., 2012	Pre-treatment *in vivo*	*Litsea glaucescens* essential oil (linalool 3.64%), β-pinene and linalool	*Litsea glaucescens* essential oil i.p. (100 and 300 mg/kg), β-pinene i.p. and linalool i.p. (100 mg/kg)	3 times (24, 18 and 1 h before behavioral tests)
Gastón *et al*., 2016	Pre-treatment *in vivo*	Coriander essential oil (linalool 81.7%) and linalool	Coriander oil i.c.v. and linalool i.c.v. (0.86, 8.6 and 86 μg/chick)	Immediately before open field test
Almeida *et al*., 2009	Pre-, co-treatment *in vivo*/co-treatment *in vitro*	Rosewood essential oil (linalool 87.7%)	Rosewood oil i.p. (100, 200 and 300 mg/kg)/rosewood oil (2, 5, 10, 50 and 100 μg/ml)	Before behavioral studies and together with pentobarbital to same tests/ incubation for 30 min
Other Biological Activities of Linalool on the Central Nervous System- Anxiolytic Activity				
References	**Experimental Model**	**Extract/Constituent**	**Concentration/Dose**	**Duration of Treatment**
Harada *et al*., 2018	Pre-, post-treatment *in vivo*	Linalool	Inhalation of linalool – 0, 20, 200 and 2.000 μl in filter paper placed at each of the 4 corners of an acryl box (25 × 25 × 25 cm)	Inhalation for 30 min before behavioral tests; after flumazenil and WAY100635 to same tests; 2 weeks after anosmia
Caputo *et al*., 2018	Pre-, post-treatment *in vivo*/co-treatment *in vitro*	Lavender essential oil (linalool 33.1%) and linalool	Lavender oil i.p. (200 mg/kg) and linalool i.p. (100 mg/kg)/lavender oil (100-400 μg/ml) and linalool (100-200 μg/ml)	30 min before experiment 1; 10 min after stress and 30 min before experiment 2; 17 days after acute or a chronic administration (once a day/10 days) 30 min before stress and 1 h 10 min before behavioral tests/cells were treated for 24 h
Linck *et al*., 2010	Pre-treatment *in vivo*	Linalool	Inhalation of linalool (1% and 3%) – sealed cylindrical (internal diameter 15 cm) glass chamber	1h of inhalation before behavioral tests
Cheng *et al*., 2015	Pre-treatment *in vivo*	Essential oil of *C. osmophloeum* ct. linalool ((+)-linalool 90%), (-)-linalool and (+)-linalool	Essential oil p.o. (250 and 500 mg/kg), (-)-linalool p.o. and (+)-linalool p.o. (500 mg/kg)	Daily for 14 days before behavioral tests

5. LINALOOL NATURAL SOURCES

Linalool is one of the constituents most found in aromatic plants' volatile concentrates, accounting for about 70% content in one thousand investigated aromatic plants [117]. Some species of fungi are also linalool producers [118]. The essential oil of rosewood (*Aniba rosaeodora* Ducke, Lauraceae) is one of the leading natural linalool sources. The species is found in the Amazon region of Brazil, Guyana, Suriname, Peru, Colombia, and Venezuela [119, 120]. In addition to rosewood, macacaporanga (*Aniba parviflora* [Meiss.] Mez), another Amazon Lauraceous species, is also a linalool source although with a lower content, ranging from 32% to 40% [120-122]. Oil of caatinga-de-mulata (*Aeollanthus suaveolens* Matt. ex Spreng., Lamiaceae), a medicinal plant cultivated in Belém, PA, Brazil, displayed linalool as a primary constituent, varying from 31.6% to 49.3% [123]. Essential oils rich in linalool (80-97%) are of great economic importance, especially for the aroma and cosmetics industry. For this reason, rosewood oil from the Amazon has been commercially explored for over 100 years [124].

Oil of coriander (*Coriandrum sativum* L., Apiaceae), an annual herbaceous from the Mediterranean and the Middle East, is another important natural source of linalool, with about 70% content [125]. It is cultivated mainly in India, North Africa, China, Europe, and Thailand and is used as a food flavoring agent [126, 127]. Besides, coriander oil has significant commercial value for its importance to the aroma industry [128]. Chemotype oils of basil (*Ocimum basilicum* L., Lamiaceae), an annual herb grown all over the world, also stands out for their high content of (-)-linalool, about 70%, which is widely used in the markets of food, pharmaceutical, cosmetic and aromatherapy [129]. The cultivation of different basil chemotypes generates various oils used in international trade [130]. Oil of lavender (*Lavandula angustifolia* Mill., Lamiaceae), an aromatic and medicinal plant originating in the Mediterranean and southern Europe, is also of great commercial importance, which presents linalool (25-38%) and linalyl acetate (25-45%) as its primary constituents [131, 132]. It is widely used in perfumes, cosmetics, food processing, and aromatherapy products [133]. The species *Cinnamomum camphora* (L.) J. Presl and *C. osmophloeum* Kaneh, natives to Southern China and Japan, have presented chemotype oils with a high linalool content (58-92%) and other chemotype oils with different primary constituents. These oils have been used as a raw material for the cosmetic and pharmaceutical industries [116, 134-137]. The oil of *Cinnamomum osmophloeum* ct. linalool, which occurs in Taiwan, has about 90% content of (+)-linalool, a significant source for aromatherapy uses [116, 138].

Linalool has long been produced in large volumes, whether from natural precursors or through chemical synthesis. For example, in 2000, half of the estimated amount of linalool was produced synthetically, while the other half was originated from aromatic plants [118]. Presently, there is a significant growth in several scientific areas with linalool as the protagonist. This fact highlights the importance of this monoterpene tertiary alcohol in the international market, in traditional medicine, in aromatherapy, and, more recently, for treating various diseases, such as depression.

CONCLUSION

In recent years, there has been considerable advancement in the knowledge of the etiology of depression. Previously, all attention was focused on the monoaminergic hypothesis of the disease. However, with scientific evolution, other pathophysiological factors started to play a prominent role. The most current hypotheses involve the close relationship between depression and environmental factors, endocrine, inflammatory, immunological, metabolic, and oxidative stress mediators, and cellular, molecular and epigenetic components of plasticity. In disease-related studies, the broader scope extends to the possibility of using natural products, interacting with different targets to become new antidepressant drugs.

In this context, linalool appears as a promising bioactive compound in the therapeutic arsenal, capable of treating depressive disorders. Studies have revealed that linalool positively interacts with a variety of pathophysiological factors involved in depression disorder. In addition, linalool potentially acts on different targets within the same etiological factor. These findings indicated several possible mechanisms of antidepressant action of linalool, a well-known natural aromatic compound. This profile of acting on multiple mechanisms on the pathophysiology of depression highlights its advantage over the conventional antidepressant treatment.

The traditional antidepressants currently used act directly on the monoaminergic pathway, mainly by inhibiting serotonin and norepinephrine reuptake. The linalool effect on several other pathways related to the pathogenesis of depression highlights its importance as an excellent candidate to integrate the medicines of clinical practice in the future. In addition, the broad spectrum of linalool mechanisms may reduce the dose required for the antidepressant response.

In this context, new studies on the mechanism of antidepressant action of linalool may focus on its pharmacokinetic profile, the use of different doses and routes of administration, and the application of different antagonists in the possible targets of the interaction with this monoterpene. Thus, it will be possible to intensify the knowledge about linalool's antidepressant activity and ultimately elucidate its pleiotropic mechanism of biological activity.

LIST OF ABBREVIATIONS

5-HT_{1A}	=	Serotonergic receptor
α_2	=	Noragrenergic receptor
α_1	=	Noragrenergic receptor
ABTS	=	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
ACTH	=	Adrenocorticotropic hormone
AKT	=	Protein kinase B
ASC	=	Apoptosis-associated speck-like protein containing a caspase-recruitment domain
BDNF	=	Brain-derived neurotrophic factor
BrdU	=	Bromodeoxyuridine
CALNN	=	Cys-Ala-Leu-Asn-Asn
CaMKII	=	Calcium-calmodulin-dependent protein kinase II
cAMP	=	Cyclic adenosine monophosphate
CNS	=	Central nervous system
COX-2	=	Cyclooxygenase 2
CRF	=	Corticotropin-releasing factor
CSF	=	Cerebrospinal fluid
DNA	=	Deoxyribonucleic acid
HO-1	=	Heme oxygenase-1
HPA	=	Hypothalamic-pituitary-adrenal

IFN-γ = Interferon-γ

IL-1 = Interleukin-1

IL-1α = Interleukin-1α

IL-1β = Interleukin-1β

IL-6 = Interleukin-6

iNOS = Inducible nitric oxide synthase

LPS = Lipopolysaccharides

LTs = Leukotrienes

MAPK = Mitogen-activated protein kinase

NF-κB = Nuclear factor kappa B

NLRP3 = Nod-like receptor family, pyrin domain containing 3

NMDA = N-methyl-d-aspartate

NO = Nitric oxide

Nos2 = Nitric oxide synthase 2

Nrf2 = Nuclear factor erythroid-2-related factor 2

PGE2 = Prostaglandins E2

PGs = Prostaglandins

TLR4 = Toll-like receptor 4

TNF-α = Tumor necrosis factor α

TrkB = Tropomyosin receptor kinase B

UVB = Ultraviolet -B

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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