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Aromatic plant-derived essential oils: bioactive compounds and their neuroprotective functions in neurological health

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Abstract

Essential oils (EOs), complex mixtures of volatile organic compounds derived from aromatic plants, have demonstrated significant therapeutic potential for neurological and psychiatric disorders through multi-targeted mechanisms. This comprehensive review synthesizes current evidence regarding the neurological effects of essential oil components, with emphasis on psychiatric disorders (depression and anxiety), sleep disorders (insomnia), and neurodegenerative diseases (particularly Alzheimer's disease). The major bioactive constituents—including monoterpenes (linalool, α-pinene, limonene, 1,8-cineole), sesquiterpenes (β-caryophyllene, patchoulol), and phenylpropanoids (cinnamaldehyde, eugenol)—exert neuroprotective effects through convergent mechanisms despite compositional diversity. These mechanisms encompass modulation of neurotransmitter systems (GABAergic, serotonergic, dopaminergic, cholinergic), regulation of the hypothalamic-pituitary-adrenal axis, anti-inflammatory and antioxidant activities, inhibition of pathological protein aggregation, enhancement of neurotrophic factor expression, and receptor-mediated neuroprotection involving GABAA and cannabinoid type 2 (CB2) receptors. The convergence of diverse phytochemical compositions on common therapeutic targets suggests potential for personalized approaches based on individual tolerability profiles, while the multi-targeted nature of EOs aligns with the multifactorial pathogenesis of neurological disorders, supporting their investigation as complementary therapeutic strategies.

Keywords: Essential oils; Neuroprotection; Depression; Anxiety; Insomnia; Alzheimer's disease; Neurotransmitter modulation; Multi-targeted therapy.

1. Introduction

Essential oils (EOs) represent a diverse class of natural aromatic compounds that have been utilized in traditional medicine systems across various cultures for thousands of years. From ancient Egyptian, Greek, Persian, and Chinese civilizations to contemporary aromatherapy practices, these volatile plant extracts have maintained their prominence in treating numerous health conditions, particularly those affecting the nervous system (Sattayakhom et al., 2023). EOs, derived from aromatic plants, are natural, concentrated, hydrophobic, and fragrant volatile liquids composed of complex compound mixtures as secondary metabolites (Lal et al., 2022). These complex chemical entities can be extracted from various plant parts including leaves, flowers, bark, seeds, roots,

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and peels through methods such as steam distillation, hydro-distillation, cold pressing, or more modern techniques including supercritical fluid extraction and microwave-assisted extraction (da Costa et al., 2022; Kowalonek et al., 2023). The chemical composition of EOs is extremely diverse, with individual oils containing dozens to hundreds of distinct compounds. For instance, tea tree oil contains more than 100 different compounds, mainly monoterpenes and their derivatives (Yang et al., 2022). Chamomile EOs comprise more than 120 chemical components, including sesquiterpenes, sesquiterpene lactones, flavonoids, and volatile compound more than 620 millions (Maleki et al., 2023). The major chemical groups found in EOs include monoterpenes, sesquiterpenes, phenylpropanoids, and various oxygenated derivatives (Zigmantaitė et al., 2022). Among these, certain compounds such as linalool, limonene, α-pinene, β-pinene, 1,8-cineole, and β-caryophyllene frequently dominate the composition and are believed to contribute significantly to the biological activities of these oils (Kamaitytė-Bukelskienė et al., 2021; Othman et al., 2023; Rasouli et al., 2023; Mwithiga et al., 2024). The lipophilic nature and relatively small molecular size of many EOs components facilitate their absorption through biological membranes, including the blood-brain barrier, enabling direct interactions with neural tissues (Hung et al., 2022).

The burden of neurological and psychiatric disorders continues to escalate globally, affecting millions of individuals and imposing substantial socioeconomic costs on healthcare systems worldwide (Shang et al., 2020; Li et al., 2022b). It is estimated that more than 620 million people worldwide suffer from depression and disorders, more than 20% of the general population experience sleep disturbances, more than 10 million people have Parkinson's disease, and more than 55 million people have Alzheimer's disease (AD) (Su et al., 2021; Fang et al., 2022; Li et al., 2022c; Shu et al., 2022; Wu et al., 2022). Conventional pharmacological treatments, while effective for many patients, are often associated with significant adverse effects, limited efficacy in certain populations, development of tolerance, and high costs. Furthermore, the side effect profiles of synthetic medications including benzodiazepines, selective serotonin reuptake inhibitors, and other psychotropic drugs have prompted increasing interest in natural alternatives that may offer therapeutic benefits with improved safety profiles (Barceló et al., 2025; Jannini et al., 2025). Recent preclinical and clinical research has demonstrated that essential oils exert measurable pharmacological effects on the central nervous system through multiple mechanisms. These include modulation of neurotransmitter systems (GABAergic, serotonergic, dopaminergic, and cholinergic pathways), regulation of the hypothalamic-pituitary-adrenal axis, anti-inflammatory and antioxidant activities, neuroprotective effects against oxidative stress and neuroinflammation, and direct interactions with various receptors and ion channels (Wei et al., 2021; Cortes-Torres et al., 2023; Xu et al., 2023a; Brinza et al., 2025; Shoji et al., 2025; Zhang et al., 2025). The olfactory pathway represents a unique route through which EOs can rapidly access brain regions involved in emotional regulation, stress response, and cognitive processing, potentially achieving swift therapeutic effects (Yin et al., 2020).

This comprehensive review synthesizes current knowledge regarding the effects of EOs on the nervous system, with specific emphasis on three major categories of neurological disorders: psychiatric disorders (depression and anxiety), sleep disorders (insomnia), and neurodegenerative diseases (particularly AD). We systematically examine the chemical composition of major EOs, elucidate their mechanisms of action at molecular, cellular, and systems levels, and identify future research priorities to advance the therapeutic application of these natural compounds in neurological medicine.

2. Major bioactive components in EOs

EOs comprise complex mixtures of volatile organic compounds, with their therapeutic properties attributed to specific bioactive constituents. Understanding the chemical nature and biological activities of these components is fundamental to elucidating their neurological effects and optimizing their therapeutic applications.

2.1. Monoterpenes

Monoterpenes, containing ten carbon atoms (C_{10}), represent the most abundant class of compounds in many EOs (Sun et al., 2022). These molecules are characterized by high volatility, lipophilicity, and the capacity to penetrate biological membranes including the blood-brain barrier (Rolf et al., 2020; Wu et al., 2025). Among monoterpenes, linalool stands as one of the most extensively studied compounds, serving as a major constituent in lavender, bergamot, and coriander EOs (Katsuyama et al., 2015; Aelenei et al., 2019; Ren et al., 2025). Linalool exists in both enantiomeric forms, with the S-(+)-linalool form commonly found in EOs demonstrating significant anxiolytic and sedative properties (Cheng et al., 2015; Bechen et al., 2022). Limonene, another prevalent monoterpene, is found in natural fruits such as grapefruit (95% content), tangerine (94%), orange (91%), mandarin orange (72%), lemon (65%), and elemi resin (50%) (González-Mas et al., 2019).Studies have shown that D - limonene has an anti - stress effect, and the anti - stress effect may stem from its potential to regulate the physiological and behavioral parameters of experimental animals (Anandakumar et al., 2021).

Pinene ($C_{10}H_{16}$) represents another important bicyclic terpene hydrocarbon featuring double bond structures (Stockmann et al., 2020; Noroozi et al., 2024). The two naturally occurring structural isomers, α-pinene and β-pinene, are among the most representative members of the monoterpene family. Each isomer exists as enantiomeric pairs [(+) and (−)], which exhibit distinct interactions with polarized light and are non-superimposable mirror images, yielding a total of four optically active forms (Vespermann et al., 2017). Both isomers are colorless liquids with distinct physicochemical properties. α-Pinene is water-insoluble but readily dissolves in oils and ethanol, exhibiting a boiling point of 155 °C. In contrast, β-pinene is oil-soluble but shows no solubility in either ethanol or water, with a boiling point of 163–166 °C (Salehi et al., 2019). β-Pinene can be commercially produced through distillation processes or by chemical transformation of α-pinene. Both α-pinene and β-pinene, either individually or in combination, have been identified in numerous plant species across diverse botanical families. Representative sources include conifers (*Pinus* spp., *Juniperus communis*, *J. oxycedrus*), culinary herbs (*Rosmarinus officinalis*, *Lavandula stoechas*, *Coriandrum sativum*, *Cuminum cyminum*), aromatic spices (*Myristica fragrans*, *Cinnamomum verum*, *Piper nigrum*, *P. guineense*), citrus species (*Citrus limon*, *C. bergamia*), and various medicinal plants (*Melaleuca alternifolia*, *Achillea millefolium*, *Artemisia capillaris*, *Ferula kuhistanica*, *F. clematidifolia*), among others (Sharopov et al., 2016; Sharifi-Rad et al., 2017; Khalifaev et al., 2018).

2.2. Sesquiterpenes

Sesquiterpenes (C_{15}), consisting of three isoprene units, are characterized by reduced volatility relative to monoterpenes and have been shown to exert pronounced protective effects on the nervous system (Forouzanfar et al., 2022; Qin et al., 2022; Wuken et al., 2023). β-Caryophyllene (BCP), a representative bicyclic ses-

quiterpene, is abundantly present in the essential oils of various food plants, including cloves, basil, and black pepper, has attracted considerable attention due to its selective agonism of cannabinoid type 2 (CB2) receptors (Varga et al., 2018; Urasaki et al., 2020). This interaction mediates anti-inflammatory and neuroprotective effects without the psychoactive properties associated with CB1 receptor activation (Ramanaiah et al., 2022; Wu et al., 2022). Studies have demonstrated that BCP exerts protective effects in various neurological disorders, including pain, anxiety, spasticity, convulsions, depression, alcoholism, and AD (Machado et al., 2018). Additionally, BCP exhibits local anesthetic-like activity, protects the nervous system against oxidative stress and inflammation, and functions as an immunomodulatory agent (Noor, 2024). Additional sesquiterpenes, exemplified by α-humulene found in hops and cannabis, exert pronounced anti-inflammatory effects by regulating microglial activation (Zaman et al., 2015; Haro-González et al., 2021; Klimek et al., 2021; Barbalace et al., 2023). This modulation is particularly significant as microglial activation constitutes a pivotal event in the neuroinflammatory processes underlying neurodegenerative diseases.

2.3. Phenylpropanoids

Phenylpropanoids are generally present as minor components in certain essential oils and are structurally characterized by a benzene ring linked to a three-carbon propyl side chain (Neelam et al., 2020). Eugenol, the primary component of clove essential oil also present in cinnamon and bay leaf oils, demonstrates multiple neuroprotective mechanisms including antioxidant activity, anti-inflammatory effects, and modulation of neurotransmitter systems (Mesole et al., 2020). Studies have shown that eugenol appears to combat oxidative stress, reduce inflammatory responses, and prevent amyloid-β (Aβ) plaque accumulation, suggesting its potential to delay the onset or progression of AD (Kakkar et al., 2025). Cinnamaldehyde, which constitutes the major constituent of cinnamon bark oil, demonstrates neuroprotective properties through multiple mechanisms, including restriction of neutrophil recruitment, inhibition of reactive oxygen species (ROS), mitigation of histological damage, and attenuation of acute hippocampal dysfunction (Kuru Bektaşoğlu et al., 2021).

2.4. Oxygenated compounds

Oxygenated monoterpenes represent another class of compounds in essential oils, such as 1,8-cineole, linalool, and α-terpineol. 1,8-Cineole, also known as eucalyptol, serves as the primary component of eucalyptus oil and appears in significant concentrations in rosemary, tea tree, and laurel oils (Jiang et al., 2021). This compound demonstrates anxiolytic and cognition-enhancing properties, with mechanisms of action including the modulation of cholinergic activity and antioxidant properties (Bahrami et al., 2023; Smach et al., 2024). Menthol, the predominant component of peppermint oil, activates transient receptor potential melastatin 8 (TRPM8) receptors, producing cooling sensations and analgesic effects (Xu et al., 2020). This mechanism underlies its efficacy in treating headaches and may contribute to its effects on alertness and cognitive function (Cabañero et al., 2025). Linalyl acetate, abundant in lavender oil alongside linalool, contributes to sedative and anxiolytic effects through similar but complementary mechanisms to its parent alcohol (Chamine and Oken, 2016; El-Tokhy et al., 2023).

The chemical diversity of EOs provides a molecular basis for their neurological effects. These bioactive compounds demonstrate favorable physicochemical properties for central nervous system access, including appropriate lipophilicity, molecular weights generally below 300 Da, and capacity to cross the blood-brain barrier through passive diffusion or direct olfactory pathways. The small molecular size and volatility of many components enable rapid absorption via inhalation, while lipophilic characteristics facilitate percutaneous penetration following topical application. Neurological and psychiatric disorders each present distinct pathophysiological features—neurotransmitter imbalances, chronic neuroinflammation, oxidative stress, synaptic dysfunction—that serve as potential therapeutic targets for EOs intervention.

3. The effects and mechanisms of EOs in nervous and mental diseases

3.1. Psychiatric disorders: depression and anxiety

Depression and anxiety disorders collectively represent the most prevalent psychiatric conditions globally, affecting over 250 million individuals and imposing substantial personal and societal burdens (Lu et al., 2022b). Major depressive disorder (MDD) is characterized by persistent dysphoric mood, anhedonia, cognitive impairment, and neurovegetative symptoms including sleep disturbance and psychomotor changes (Li et al., 2022a). The neurobiological underpinnings involve complex interactions among neurotransmitter systems, neuroendocrine dysfunction, and cellular pathology (Pike et al., 2022).

Deficiencies in serotonergic, noradrenergic, and dopaminergic neurotransmission contribute to depressive symptomatology, with reduced synaptic availability of these monoamines resulting from decreased synthesis, increased reuptake, or excessive degradation by monoamine oxidase enzymes (Shewale et al., 2012; Bosnjak Kuharic et al., 2019). Beyond monoaminergic dysfunction, chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis represents a cardinal neuroendocrine feature of depression (Menke, 2024). Sustained hypersecretion of corticotropin-releasing hormone from hypothalamic neurons drives excessive adrenocorticotropic hormone release from the pituitary, culminating in elevated cortisol production (Eriksson et al., 2023). Chronic hypercortisolemia exerts deleterious effects on hippocampal neurons, impairing neuroplasticity, reducing neurogenesis in the dentate gyrus, and causing dendritic atrophy (Fang et al., 2020). Glucocorticoid receptor resistance develops with prolonged exposure, disrupting normal negative feedback regulation and perpetuating HPA axis hyperactivity (Ganesan et al., 2024). GABAergic innervation normally inhibits CRH secretion in the paraventricular nucleus, but decreased GABAergic tone in depression weakens this inhibitory control, contributing to HPA axis overactivation (Colmers and Bains, 2018). Furthermore, pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, are significantly upregulated in depressed patients and contribute to serotonin depletion through indoleamine 2,3-dioxygenase (IDO) activation, which diverts tryptophan metabolism from the serotonergic pathway toward kynurenine production. Additionally, these inflammatory mediators downregulate brain-derived neurotrophic factor (BDNF) expression, consequently impairing neuronal survival, synaptic plasticity, and adult neurogenesis (Beurel et al., 2020; Zhang et al., 2020; Lu et al., 2022a).

Anxiety disorders, while overlapping with depression in some neurobiological features, exhibit distinct pathophysiological characteristics. GABAergic neurotransmission dysfunction represents a central mechanism underlying anxiety symptomatology. Gamma-aminobutyric acid (GABA), the primary inhibi-

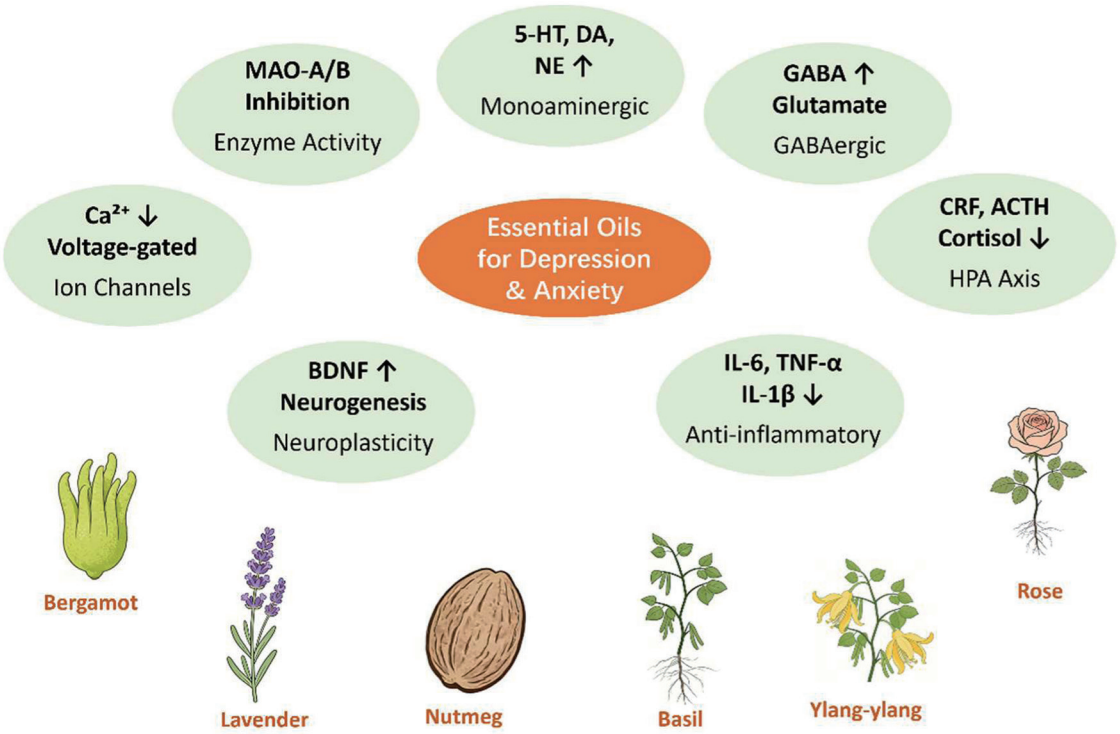

Figure 1. The effects of EOs on depression and anxiety.

tory neurotransmitter in the mammalian central nervous system, regulates neuronal excitability through GABA_A and GABA_B receptor activation (Lydiard, 2003; Zhu et al., 2018). Diminished GABAergic inhibition in anxiety-related neural circuits including the amygdala, prefrontal cortex, and bed nucleus of the stria terminalis results in excessive neuronal activation and heightened fear responses (Yu et al., 2022; Wang et al., 2023; Chen et al., 2024a; Li et al., 2024a). Serotonergic dysfunction also contributes to anxiety pathophysiology, with the 5-HT1A receptor subtype playing particularly important roles in anxiety regulation through autoreceptor-mediated control of serotonergic neuronal firing and postsynaptic effects on amygdala and hippocampal function (Stiedl et al., 2015). There exists complex regulatory relationships between neurotransmitter systems, with serotonin modulating prefrontal cortex functions via regulation of GABA_A receptor-mediated inhibitory transmission and directly regulating dopamine release through actions on dopaminergic neurons or ventral tegmental area GABAergic and glutamatergic neurons (Tan et al., 2004; Di Giovanni et al., 2010).

Current pharmacological interventions target these neurobiological mechanisms but suffer from significant limitations that motivate investigation of complementary approaches. The therapeutic limitations of conventional treatments, combined with patient preferences for natural interventions and concerns about pharmaceutical adverse effects, have prompted systematic investigation of EOs as potential complementary or alternative therapeutic approaches for psychiatric disorders. EOs address psychiatric disorders through multi-level mechanisms operating across neurotransmitter systems, neuroendocrine pathways, inflammatory processes, and neuroplasticity regulation (Figure 1). The convergence of these mechanisms provides therapeutic effects relevant to both depression and anxiety, conditions that frequently co-occur and share overlapping neurobiological substrates.

3.1.1. Monoaminergic neurotransmitter system modulation

Central monoamine neurotransmitter abnormalities represent core pathophysiological features addressable by essential oils. Multiple studies demonstrate that EOs administration increases brain concentrations of serotonin, norepinephrine, and dopamine in depression-relevant regions. Ligusticum wallichii essential oil increases dopamine in hippocampus and norepinephrine in prefrontal cortex and striatum of chronic stress-induced depression model rats (Ling et al., 2019). The mechanisms involve both enhanced synthesis and reduced degradation, with Myristica fragrans essential oil demonstrating monoamine oxidase inhibition that reduces neurotransmitter breakdown and consequently increases brain serotonin, dopamine, and norepinephrine levels (Zhang et al., 2021). Asarum essential oil increases serotonin, glutamate, and GABA levels through mechanisms resembling fluoxetine hydrochloride (Pu et al., 2018), while individual monoterpene components including linalool and β-pinene produce antidepressant effects through direct monoaminergic system interactions (Guzmán-Gutiérrez et al., 2015). Pharmacological dissection studies employing receptor-specific antagonists elucidate the precise receptor subtypes mediating essential oil effects. The antidepressant action of lemon essential oil is blocked by buspirone (5-HT1A agonist), DOI (5-HT2A agonist), and mianserin (5-HT2A/C antagonist), while reserpine completely blocks its effects, indicating involvement of both serotonergic and noradrenergic systems (Hao et al., 2013). For anxiety, lavender essential oil's effects are blocked by the 5-HT1A antagonist WAY-100635 but not by GABA_A antagonists, demonstrating primary serotonergic mediation (Chioca et al., 2013). Conversely, carvacryl acetate's anxiolytic effect is reversed by flumazenil but not WAY-100635, confirming direct GABA_A receptor mediation, while lemongrass oil's action is blocked by picrotoxin but not

WAY-100635 (de Moraes Pultrini et al., 2006; Chioca et al., 2013). This receptor selectivity variation explains differential therapeutic profiles across EOs, with some primarily targeting serotonergic systems and others engaging GABAergic mechanisms.

3.1.2. GABAergic and glutamatergic neurotransmission

Beyond classical neurotransmitters, EOs modulate amino acid neurotransmitter systems critical for anxiety regulation. Bergamot essential oil significantly elevates extracellular concentrations of aspartate, glycine, and taurine following intraperitoneal administration. When perfused into rat hippocampus, bergamot oil increases both GABA and glutamate levels, maintaining the critical excitatory-inhibitory balance (Morrone et al., 2007). At high concentrations, bergamot oil-induced glutamate release is prevented by glutamate transporter blockers, suggesting monoterpene hydrocarbons stimulate release through transporter reversal mechanisms. Linalool affects glutamate release and reuptake in vitro, while α-asarone downregulates GluR1-containing AMPA receptors and NR2A-containing NMDA receptors while upregulating GABA_A receptors in the basolateral amygdala, a region critical for emotional regulation (Silva Brum et al., 2001; Tian et al., 2017).

3.1.3. HPA axis regulation and neuroendocrine effects

HPA axis dysregulation characteristic of depression and anxiety is normalized by EOs at multiple regulatory levels (Zhang and Yao, 2019; Zhang et al., 2021). Agarwood essential oil reduces corticotropin-releasing factor gene expression and significantly inhibits CRF receptor transcription and protein expression in cerebral cortex and hippocampus, while downstream decreasing adrenocorticotropic hormone and cortisol concentrations (Wang et al., 2018). Bergamot essential oil attenuates corticosterone responses to acute elevated plus maze stress and participates in HPA axis regulation by modulating GABAergic neurotransmission (Saiyudthong and Marsden, 2011). S-limonene reduces serum corticosterone and inhibits HPA axis activity through mechanisms potentially mediated by GABA receptors (Zhou et al., 2009). Ylang-ylang essential oil reverses corticosterone changes induced by the 5-HT2C agonist mCPP[84], demonstrating integration of serotonergic and HPA axis modulation (Zhang et al., 2016). Clinical studies have shown that inhaling rose oil can reduce the concentration of oxygenated hemoglobin in the right prefrontal cortex, indicating physiological relaxation (Igarashi et al., 2014). The reason may be related to mediating the downstream effects of the HPA axis.

3.1.4. Anti-inflammatory and neuroprotective mechanisms

Inflammatory mechanisms contribute importantly to depression and anxiety pathophysiology, with EOs demonstrating robust anti-inflammatory effects. Purple perilla essential oil significantly reduces IL-6, IL-1β, and TNF-α in hippocampus of chronic stress model mice, with these effects occurring concurrently with increased 5-HIAA and serotonin (Ji et al., 2014). Styrax essential oil inhalation produces antidepressant and anxiolytic effects accompanied by reduced serum angiotensin, IL-6, and TNF-α (Liang et al., 2018). Geraniol inhibits NF-κB pathway activation and regulates NLRP3 inflammasome expression (Deng et al., 2015). By targeting upstream inflammatory mechanisms, EOs may prevent cascades perpetuating psychiatric pathology. Neuroplasticity enhancement provides additional therapeutic mechanisms addressing stress-induced neuronal damage. Basil volatile oil reduces corticosterone while upregulating BDNF and glucocorticoid receptor expression, reducing hippocampal neuronal atrophy and apoptosis, and increasing astrocyte and neuron numbers (Murárikova et al., 2017). Cananga odorata essential oil suppresses ERK phosphorylation and downstream CREB phosphorylation and c-Fos expression in hippocampus (Zhang et al., 2018), while vetiver essential oil increases c-Fos expression in central amygdaloid nucleus (Saiyudthong et al., 2015), demonstrating MAPK pathway involvement in anxiolytic effects.

3.1.5. Ion channel modulation and electrophysiological effects

Additional mechanisms include voltage-gated calcium channel modulation, with Silexan non-selectively reducing calcium influx through N-, P/Q-, and T-type channels, dampening neuronal excitability and neurotransmitter release under anxiety conditions (Schuwald et al., 2013). Electroencephalographic studies reveal that EOs modulate cortical activity patterns associated with emotional states. Bergamot oil increases alpha and beta rhythms in hippocampus and theta and alpha bands in cortex, while geraniol increases delta wave percentage (Rombolà et al., 2009; Medeiros et al., 2018). Lavender inhalation decreases alpha-1 waves at parietal and posterior temporal regions in comfortable subjects (Masago et al., 2000). Changes in left frontal alpha activity correlate with anxiety symptom reduction, suggesting EEG measures may serve as biomarkers of essential oil anxiolytic effects (Moscovitch et al., 2011).

Beyond their effects on mood and anxiety, EOs also demonstrate therapeutic potential in related neurological conditions, particularly sleep disorders, which share common neurobiological substrates with psychiatric conditions.

3.2. Sleep disorders and insomnia

Sleep disorders, particularly insomnia, affect approximately 30% of adults globally, with chronic insomnia characterized by difficulty initiating sleep, maintaining sleep, or early morning awakening occurring at least three times weekly for three months or longer and causing daytime impairment (Germain et al., 2021; Hammad et al., 2022). The neurobiological architecture governing sleep-wake regulation involves homeostatic and circadian processes mediated by multiple neurotransmitter systems. The homeostatic process is driven by adenosine accumulation during wakefulness, generating increasing sleep pressure proportional to prior wake duration (Wang et al., 2022a). Adenosine binds to A1 and A2A receptors in sleep-regulatory brain regions, inhibiting histaminergic neurons while activating sleep-promoting GABAergic neurons in the ventrolateral preoptic nucleus (Pelluru et al., 2016; Guo et al., 2020; Shao et al., 2020). GABAergic neurotransmission constitutes the principal sleep-promoting mechanism. GABAergic neurons in the ventrolateral preoptic nucleus directly inhibit arousal-promoting regions including the tuberomammillary nucleus, locus coeruleus, and dorsal raphe nucleus, forming a "flip-flop" switch that generates discrete wake and sleep states (Zhang et al., 2022). Reduced GABAergic tone leads to inadequate inhibition of arousal systems, with studies showing that peripheral blood expression levels of GABA_A receptor α1 and α2 subunit mRNA differ significantly between sleep disorder patients and healthy individuals (Xiang et al., 2023).

Beyond immediate neurotransmitter-mediated sleep-wake switching, sleep regulation involves coordinated circadian timing and neuropeptide systems that maintain stable arousal states.

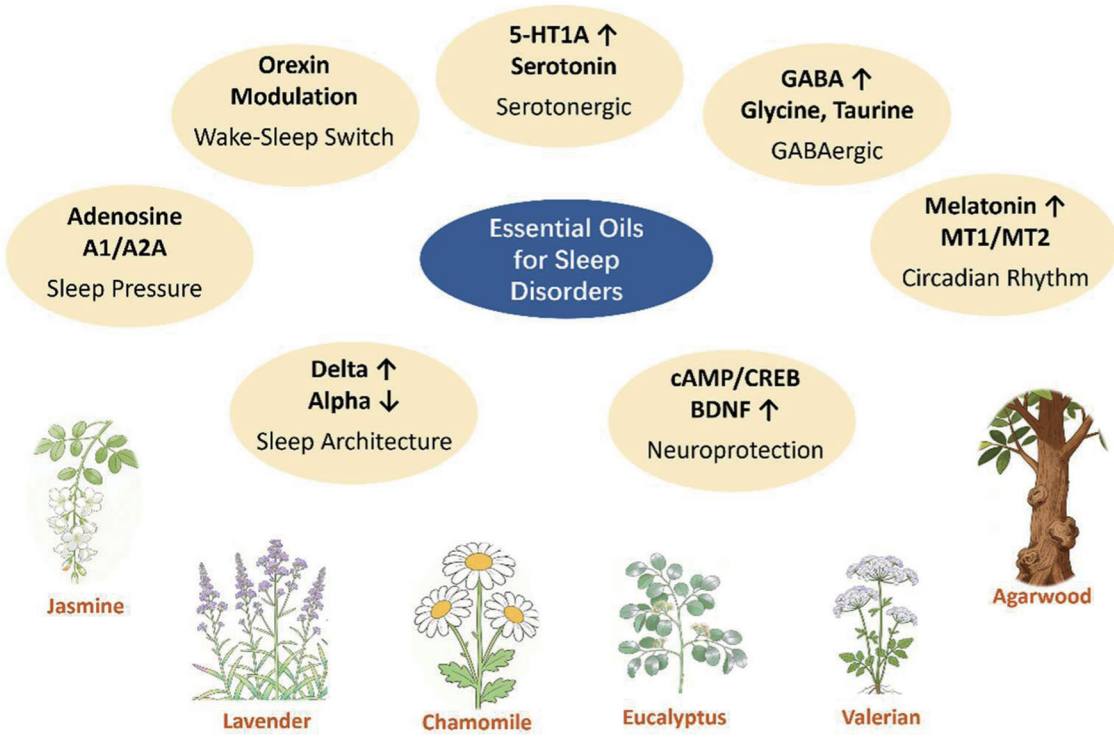

Figure 2. The effects of EOs on sleep disorders.

The circadian timing system, orchestrated by the suprachiasmatic nuclei (SCN), synchronizes endogenous biological rhythms to the 24-hour light-dark cycle through light input via the retinohypothalamic tract and temporal cues from melatonin secretion (Lamba et al., 2014). Melatonin, synthesized in the pineal gland from serotonin, exhibits a robust circadian rhythm with peak secretion during darkness (Hsiao et al., 2019). Melatonin binding to MT1 and MT2 receptors in the SCN conveys the signal of darkness to the biological clock, with MT1 activation decreasing wake-promoting activity and MT2 activation inducing phase shifts in circadian timing (Yoon et al., 2020). In addition, the orexin (hypocretin) neuropeptide system, plays a central role in stabilizing wakefulness and preventing inappropriate transitions between sleep and wake states (Beuckmann et al., 2019). Orexinergic neurons release orexin-A and orexin-B peptides that activate noradrenergic, histaminergic, serotonergic, and cholinergic arousal systems while modulating motivation, stress responses, and energy metabolism (Saper et al., 2005; Muehlan et al., 2023). In insomnia, dysregulated orexin signaling may contribute to hyperarousal states characterized by elevated cortical activation and impaired sleep onset despite adequate homeostatic sleep pressure. Serotonergic neurotransmission exhibits complex, state-dependent effects on sleep-wake regulation. Serotonergic neurons demonstrate highest firing rates during wakefulness, reduced activity during NREM sleep, and minimal activity during REM sleep (Kato et al., 2022). Serotonin serves as the metabolic precursor for melatonin synthesis, establishing a direct biochemical link between daytime arousal and nighttime sleep promotion (Lee et al., 2021). Serotonin modulates sleep architecture through diverse receptor subtypes, with 5-HT2A receptor activation increasing wakefulness and reducing slow-wave sleep (Vanover and Davis, 2010).

At the cellular level, chronic insomnia is increasingly recognized as involving metabolic dysregulation and oxidative-inflammatory processes that interact bidirectionally with neurotransmitter and circadian systems to perpetuate sleep disturbance. Emerging evidence implicates oxidative stress, neuroinflammation, and mitochondrial dysfunction as fundamental pathophysiological mechanisms underlying chronic insomnia, with these processes intimately linked to circadian clock dysregulation. Mitochondrial rhythms, synchronized by circadian clock genes, are essential for maintaining redox balance, and circadian disruption increases ROS production in sleep-regulatory brain regions, impairing neuronal firing and melatonin secretion (Silver et al., 2012; Solt et al., 2012). Elevated ROS inhibits circadian clock gene transcription, creating a vicious cycle that exacerbates circadian disruption and sleep fragmentation (Early et al., 2018). Beyond damaging effects, ROS also act as signaling molecules modulating inflammatory responses and neuronal excitability implicated in sleep regulation (Castillo-Vazquez et al., 2025). This oxidative burden activates NF-κB signaling cascades, initiating transcription of pro-inflammatory genes and establishing a self-perpetuating cycle of inflammation and sleep disruption.

These multifaceted pathophysiological mechanisms—spanning neurotransmitter imbalance, circadian dysregulation, and metabolic dysfunction—provide the neurobiological framework for understanding how essential oils achieve therapeutic effects in insomnia through complementary mechanisms that restore sleep-wake homeostasis (Figure 2). Based on this pathophysiological understanding, EOs demonstrate therapeutic efficacy through multiple complementary mechanisms.

3.2.1. GABAergic and serotonergic neurotransmission enhancement

Enhancement of GABAergic neurotransmission represents a pri-

mary mechanism through which EOs promote sleep initiation and maintenance. Multiple studies demonstrate that essential oil administration increases brain GABA concentrations and enhances GABAergic receptor function in sleep-relevant neural circuits. Lavender essential oil fractions significantly elevate hippocampal GABA levels following inhalation exposure, with complementary effects on sleep architecture—light fractions enriched in linalool and trans-β-ocimene contributing preferentially to sleep maintenance, while heavy fractions containing linalyl acetate, lavandulyl acetate, and trans-caryophyllene demonstrating superior effects on sleep onset (Xu et al., 2023a). Eucalyptus essential oil intervention increases brain concentrations of GABA, glycine, and taurine—all inhibitory neurotransmitters that reduce neuronal excitability and promote sleep (Li et al., 2024b). This GABAergic enhancement operates synergistically with serotonergic pathway modulation to achieve comprehensive sleep regulation.

The serotonergic system plays a central role in essential oil-mediated sleep promotion, with valerian essential oil exerting hypnotic effects primarily through the serotonergic synapse pathway. In PCPA-induced insomnia rats, valerian essential oil significantly prolonged sleep duration and alleviated anxiety-related behaviors through mechanisms involving the active component caryophyllene, which upregulates 5-HT1A receptor expression, enhancing central serotonin activity and release (Wang et al., 2022b). Similarly, beta-myrcene, identified as a primary sedative-hypnotic component in lavender essential oil, operates through analogous serotonergic mechanisms. In PCPA-induced insomnia mice, beta-myrcene treatment enhanced the hypnotic effect of anobarbital sodium by prolonging sleep duration, decreasing sleep latency, and increasing sleep onset rate, while reducing hypothalamic neuronal damage and elevating neurotransmitter levels of GABA, 5-HT, and glutamate in both serum and hypothalamus (Chen et al., 2024b). Network pharmacology analysis confirmed that beta-myrcene upregulates genes and proteins in the serotonergic synaptic pathway, supporting its potential as a clinical candidate for insomnia management. Comparative analysis of five EOs (Jasminum sambac, Magnolia denudata, Rosa rugosa, Aloysia citriodora, and Abies balsamea) in PCPA-induced insomnia mice revealed converging mechanisms despite compositional diversity, with all EOs upregulating 5-HT1A and GABAARα1 expression. These oils contained terpenoid-rich compositions including α-farnesene (28.42%), linalool (68.84%), and citronellol (23.78%), and promoted neuronal preservation in multiple brain regions (Feng et al., 2024). Notably, A. citriodora and A. balsamea essential oils exhibited pronounced upregulation of 5-HT1A protein, while J. sambac and M. denudata showed distinct receptor modulation profiles, suggesting that while serotonergic and GABAergic pathways represent common therapeutic targets, individual EOs demonstrate receptor subtype selectivity that may confer distinct clinical profiles.

3.2.2. Neuroprotective pathways and neurotransmitter homeostasis

Beyond classical neurotransmitter modulation, EOs engage neuroprotective pathways critical for sleep regulation under pathological conditions. Huoermai essential oil (HEO), a traditional Tibetan therapy comprising Myristica fragrans and Carum carvi, demonstrates efficacy in plateau insomnia through the cAMP/CREB/BDNF/GABAergic pathway. In intermittent hypobaric hypoxia-induced plateau insomnia mice, HEO ameliorated neuronal damage in cortex, hippocampus, thalamus, and hypothalamus regions (Yang et al., 2025). ELISA analysis revealed that HEO increased GABA and melatonin levels while reducing serotonin and adenosine concentrations in brain tissue, indicating normalization of sleep-wake regulatory neurotransmitters. This pathway represents a critical neuroprotective mechanism wherein EOs modulate neuronal survival, anti-apoptotic signaling, and synaptic plasticity concurrently with sleep regulation, particularly relevant in insomnia secondary to metabolic stress or hypoxic conditions. The therapeutic effects extend to restoration of neurotransmitter homeostasis disrupted in chronic insomnia states. Moringa seed essential oil, rich in oleic acid, palmitoleic acid, stigmasterol, and γ-stigmasterol, demonstrates sedative-hypnotic effects through neurotransmitter rebalancing in PCPA-induced insomnia rats. Aromatherapy with Moringa seed essential oil at concentrations of 10%, 5%, and 2.5% reduced locomotor activity, increased exploratory interest, enhanced serum 5-HT levels, and elevated hypothalamic GABA content without the motor impairment characteristic of benzodiazepines, suggesting selective modulation of arousal-related neurocircuitry rather than global CNS depression (Wei et al., 2024). This distinction is critical, as conventional sedative-hypnotics achieve sleep promotion through non-selective neuronal inhibition, whereas EOs appear to restore physiological neurotransmitter balance conducive to natural sleep architecture.

3.2.3. Electrophysiological modulation and sleep architecture

EOs produce distinct electrophysiological signatures that further differentiate their mechanisms from conventional hypnotics. Single-blind studies in healthy subjects demonstrated that lavender aromatherapy during sleep reduced alpha wave activity during wake stages while increasing delta wave power during slow-wave sleep (SWS) (Ko et al., 2021). Quantitative EEG analysis revealed that lavender promoted SWS occurrence and reduced sleep interruptions, as evidenced by decreased alpha power across multiple brain regions. This electrophysiological profile contrasts sharply with benzodiazepines, which suppress delta activity and disrupt normal sleep architecture, potentially impairing the restorative functions of sleep. Participants exposed to lavender aromatherapy reported improved subjective sleep quality and enhanced daytime vigor, suggesting that the electrophysiological changes translate to meaningful improvements in sleep-related functional outcomes.

3.2.4. Long-term efficacy and safety profile

In addition, one advantage of essential oil therapy lies in sustained efficacy without tolerance development, addressing a fundamental limitation of conventional sedative-hypnotics. Agarwood (Aquilaria species) essential oil demonstrates this property definitively in comparative studies with diazepam. Different agarwood preparations (aqueous extracts, alcoholic extracts, and volatile oils) significantly increased sleep rate, prolonged sleep duration, and shortened sleep latency in pentobarbital synergy models (Wang et al., 2016). Critically, following 1–2 weeks of administration to insomnia mice, diazepam-treated groups exhibited diminished or abolished hypnotic effects characteristic of benzodiazepine tolerance, whereas agarwood essential oil-treated groups maintained consistent efficacy without significant drug resistance (Wang et al., 2017). The active compounds benzylacetone, calarene, and jinkoheremol possess significant CNS activity and constitute the material basis for agarwood's sedative-tranquilizing properties (Chen et al., 2022). EOs demonstrate multi-targeted therapeutic mechanisms for insomnia through modulation of neurotransmitter systems, neuroprotection, and electrophysiological regulation, offering advantages over conventional sedative-hypnotics in safety profile

and absence of tolerance development. These findings in psychiatric and sleep disorders provide a foundation for investigating essential oil applications in neurodegenerative diseases, where similar pathophysiological mechanisms may be therapeutically targeted.

3.3. Neurodegenerative diseases

Neurodegenerative diseases encompass progressive neurological disorders characterized by selective neuronal loss, protein aggregation, synaptic dysfunction, and cognitive or motor impairment (Wallach et al., 2021). AD, affecting over 50 million individuals worldwide with projections estimating 152 million cases by 2050, represents the most prevalent neurodegenerative disorder (Chang et al., 2023; Yoon et al., 2024). Given its high prevalence, well-established pathological features, and extensive preclinical evidence base, AD may serve as the primary focus of essential oil research in neurodegenerative conditions.

AD is characterized by progressive cognitive decline, memory impairment, and behavioral disturbances accompanied by distinctive neuropathological hallmarks: extracellular Aβ peptide accumulation forming senile plaques, intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, and progressive neuronal loss particularly affecting the hippocampus and cortical regions critical for memory and executive function (Srimaharaj, 2026). Aberrant processing of amyloid precursor protein generates neurotoxic Aβ peptides that oligomerize and aggregate, disrupting neuronal function and triggering inflammatory responses (Reda et al., 2024). Concurrently, hyperphosphorylated tau protein dissociates from microtubules and forms neurofibrillary tangles, destabilizing the neuronal cytoskeleton and impairing axonal transport, ultimately leading to neuronal degeneration (Yook et al., 2024).

The cholinergic hypothesis postulates that dementia correlates with diminished acetylcholine (ACh) concentrations and degeneration of cholinergic neurons in the brain (Hu et al., 2024). Acetylcholinesterase (AChE), the enzyme responsible for ACh hydrolysis at synaptic clefts, represents an important therapeutic target (Liu et al., 2022). Current first-line pharmacological interventions—AChE inhibitors including donepezil, rivastigmine, and galantamine—are able to stabilize or slow decline in cognition, function, and behavior by enhancing cholinergic neurotransmission, but demonstrate only modest benefits without halting disease progression and are associated with adverse effects, particularly gastrointestinal disturbances (Hansen et al., 2008).

Beyond cholinergic deficits and protein pathology, AD pathogenesis involves multiple convergent mechanisms. Oxidative stress, characterized by elevated reactive oxygen species (ROS) production, increased lipid peroxidation, and protein oxidation, renders neurons particularly vulnerable given the brain's high metabolic rate and limited antioxidant defenses (Araújo-Rodrigues et al., 2025). Neuroinflammation, mediated by activated microglia and reactive astrocytes, releases pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6 that impair synaptic function and promote pathological protein aggregation (Fazal et al., 2026). Mitochondrial dysfunction, particularly impaired electron transport chain function, reduces ATP production while increasing ROS generation, further exacerbating oxidative damage (Shekarian et al., 2023). Additionally, reduced expression of brain-derived neurotrophic factor (BDNF) compromises neuronal survival and synaptic plasticity, with BDNF depletion correlating with cognitive decline in affected brain regions (Tang et al., 2026).

Current pharmacological approaches targeting single pathways have demonstrated limited disease-modifying effects. The recent failures of numerous candidates, including antibody therapies that successfully reduce amyloid burden without commensurate cognitive benefits, have necessitated exploration of alternative therapeutic strategies. The multifactorial pathogenesis of AD suggests that multi-targeted therapeutic approaches may prove more effective than single-target interventions. EOs, with their complex phytochemical compositions conferring simultaneous antioxidant, anti-inflammatory, anticholinesterase, anti-aggregation, and neuroprotective properties, represent promising candidates for complementary or adjunctive therapy (Figure 3). The preponderance of preclinical evidence focuses on AD given its prevalence and the availability of well-validated experimental models, though emerging data suggest potential efficacy in other neurodegenerative conditions including Parkinson's disease sharing common pathogenic mechanisms. These pathophysiological insights establish the foundation for understanding how essential oils engage multiple therapeutic targets simultaneously to potentially modify neurodegenerative disease progression.

3.3.1. Cholinergic enhancement and monoamine modulation

Acetylcholinesterase inhibition represents a well-established mechanism through which EOs enhance cholinergic neurotransmission and potentially ameliorate cognitive symptoms in AD. Lavender essential oils displayed anticholinesterase activity against both AChE and butyrylcholinesterase (BChE), along with antioxidant properties characterized by free radical scavenging activity against DPPH, ABTS, and hydrogen peroxide (Hancianu et al., 2013). Cistus species essential oil also demonstrated antioxidant and cholinesterase inhibitory activities relevant to AD prevention and treatment. Comprehensive phytochemical characterization identified diverse terpene compositions including epi-13-manoyl oxide, kaur-16-ene, and (E)-α-ionone as prominent constituents, with compositional variations among different Cistus species (*C. creticus, C. salvifolius, C. libanotis, C. monspeliensis, C. villosus*). The EOs exhibited significant free radical scavenging activities in multiple complementary assays (DPPH, ABTS, hydrogen peroxide) and demonstrated significant AChE and BChE inhibitory activities, suggesting potential to enhance cholinergic neurotransmission while simultaneously providing antioxidant neuroprotection (Loizzo et al., 2013). Cinnamomum zeylanicum essential oil, containing cinnamaldehyde (81.39%) and cinnamyl acetate (4.20%) as primary constituents, demonstrated comprehensive multi-targeted activities. *In vitro* cholinesterase inhibition assays revealed potent AChE and BChE inhibitory effects exceeding 99.0%, with specific inhibitory activities of 278.72 μg gallic acid equivalents/g samples for AChE and 330.72 μg gallic acid equivalents/g samples for BChE. Systematic evaluation of different cinnamaldehyde to cinnamyl acetate ratios revealed synergistic interactions, with specific combinations producing enhanced cholinesterase inhibition exceeding the additive effects of individual components. Importantly, the essential oil demonstrated monoamine oxidase-A (MAO-A) and monoamine oxidase-B (MAO-B) inhibition exceeding 96%, suggesting potential mood-enhancing and neuroprotective effects through preservation of neurotransmitters including serotonin, dopamine, and norepinephrine (Sihoglu Tepe and Ozaslan, 2020).

Beyond the extensively characterized EOs, additional botanicals demonstrate cholinergic modulatory properties relevant to AD therapeutics. EOs from Rosmarinus officinalis exhibit AChE regulatory activity alongside its capacity to mitigate oxidative damage, with bioactive constituents including 1,8-cineole, camphor, and α-pinene contributing to enhanced neurotransmission and main-

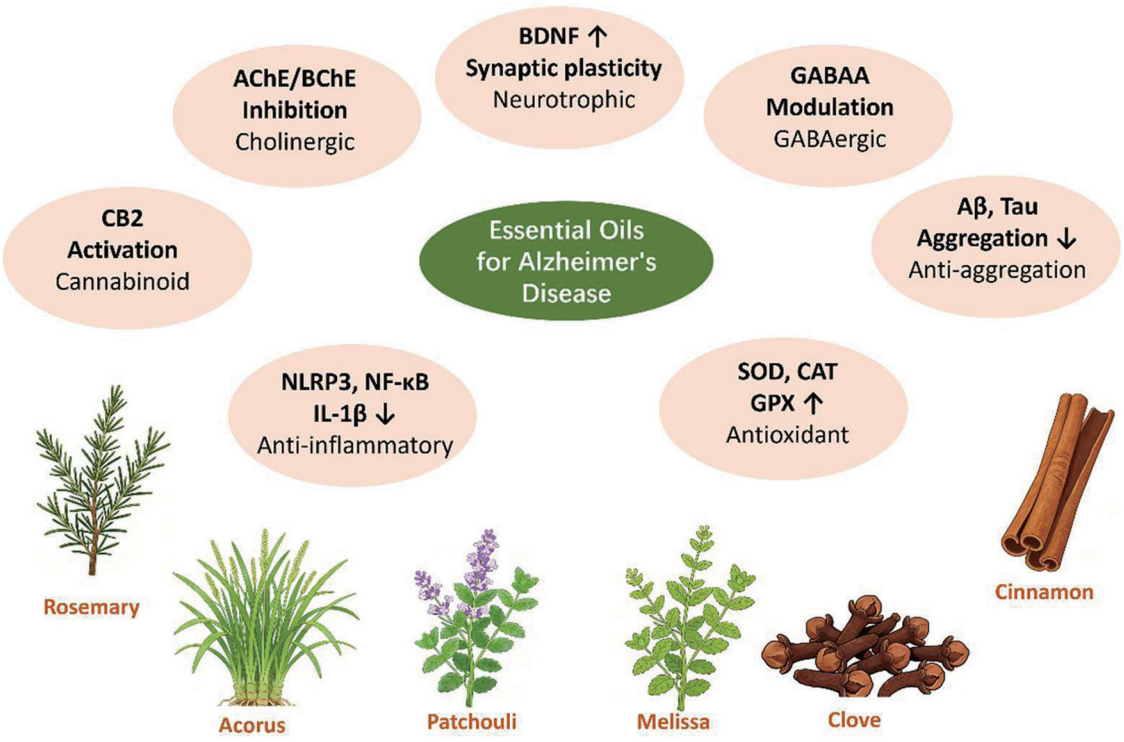

Figure 3. The effects of EOs on neurodegenerative diseases.

tenance of synaptic plasticity (Habtemariam, 2016; Ghasemzadeh Rahbardar and Hosseinzadeh, 2020). Similarly, Melissa officinalis essential oil, characterized by high citral content, ameliorates cognitive deficits through dual mechanisms involving AChE inhibition and antioxidant-mediated cellular protection (Kiani, 2016). These botanicals expand the therapeutic repertoire of EOs with documented cholinergic enhancement capabilities, reinforcing the concept that diverse phytochemical compositions can converge on common therapeutic targets while potentially offering distinct pharmacological profiles.

3.3.2. Anti-amyloid and anti-tau mechanisms

Beyond enhancing neurotransmission, EOs demonstrate capacity to interfere with pathological protein aggregation, addressing core neuropathological features of AD. Cinnamomum zeylanicum essential oil and its constituents inhibited Aβ1-42 aggregation in vitro, with specific component ratios demonstrating amplified anti-aggregation effects indicative of synergistic mechanisms (Sihoglu Tepe and Ozaslan, 2020). Thymus vulgaris essential oil, rich in the phenolic monoterpenes thymol and carvacrol, demonstrates multifaceted neuroprotective actions encompassing anti-aggregation properties (Asadbegi (Hamedi) et al., 2023). Zataria multiflora boiss essential oil, a traditional Persian medicinal plant containing thymol, linalool, carvacrol, and flavonoids as principal bioactive compounds, demonstrated efficacy in ameliorating cognitive deficits in Aβ1-42-induced AD rat models (Majlessi et al., 2012). Acorus tatarinowii Schott essential oil, containing α-asarone, β-asarone, and γ-asarone as principal constituents, demonstrated efficacy in attenuating neuroinflammation through NLRP3 inflammasome inhibition in 3×Tg-AD transgenic mice (a model recapitulating both amyloid and tau pathology). Mechanistically, A. tatarinowii essential oil suppressed NLRP3 inflammasome activation, consequently reducing production and secretion of IL-1β, IL-6, and TNF-α in hippocampus. Critically, the essential oil significantly mitigated tau protein hyperphosphorylation at multiple epitopes, with reduced phosphorylated tau levels in cortex and hippocampus. These effects operated through inhibition of NF-κB signaling pathway, with reduced nuclear translocation of NF-κB p65 subunit (Xu et al., 2023b).

In addition, several additional EOs demonstrate capacity to interfere with pathological protein processes central to AD pathogenesis. Origanum vulgare essential oil, characterized by elevated concentrations of the phenolic monoterpenes carvacrol and thymol, exhibits pronounced anti-amyloid activity by preventing Aβ peptide oligomerization and subsequent fibril formation (Gürbüz et al., 2019). Complementing these anti-amyloid effects, Syzygium aromaticum essential oil, dominated by the phenylpropanoid eugenol alongside sesquiterpene β-caryophyllene, demonstrates inhibition of advanced glycation end product (AGE) formation (Suantawee et al., 2015). By preventing AGE formation, clove essential oil may address a parallel protein modification pathway that intersects with and potentially exacerbates classical amyloid and tau pathologies.

3.3.3. Antioxidant defense and anti-inflammatory mechanisms

EOs enhance endogenous antioxidant defenses while simultaneously reducing oxidative damage markers, addressing oxidative stress pathology central to AD progression. Tetraclinis articulata essential oil, composed predominantly of α-pinene, camphor, L-bornyl acetate, and limonene, demonstrated significant neuroprotective effects in Aβ1-42-induced AD rat models. Biochemical analysis demonstrated enhanced activities of superoxide dis-

mutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) in hippocampus, while simultaneously reducing protein carbonyl and malondialdehyde levels, markers of protein oxidation and lipid peroxidation respectively. The essential oil also modulated hippocampal AChE activity, suggesting restoration of cholinergic neurotransmission (Sadiki et al., 2019).

Boswellia carterii essential oil, obtained from tree resin and containing the monoterpene α-pinene, monoterpene limonene, and sesquiterpene β-caryophyllene, attenuates neuroinflammation while promoting neuronal viability (Burns et al., 2007; Al-Yasiry and Kiczorowska, 2016; Hussain et al., 2022). Zingiber officinale essential oil, characterized by sesquiterpene constituents α-zingiberene and β-sesquiphellandrene, counters oxidative stress alongside anti-inflammatory effects that moderate glial activation (Feng et al., 2011; Mathew and Subramanian, 2014). Eucalyptus globulus essential oil, containing predominantly the oxygenated monoterpene 1,8-cineole with minor contributions from α-pinene and limonene, exhibits similar capacity to enhance endogenous antioxidant defenses while reducing oxidative damage markers, with the mechanistic effects potentially involving both direct radical scavenging and transcriptional upregulation of antioxidant enzyme genes (Harkat-Madouri et al., 2015; Bey-Ould Si Said et al., 2016; Assaggaf et al., 2022).

3.3.4. Neurotrophic factor modulation and receptor-mediated neuroprotection

Neurotrophic factor modulation represents a critical neuroprotective mechanism engaged by EOs that addresses neuronal survival and synaptic dysfunction underlying cognitive decline in AD. Pogostemon cablin essential oil, characterized by the sesquiterpene alcohol patchoulol (32–40%) along with sesquiterpenes α-bulnesene (12–20%) and α-guaiene (5–9%), enhances BDNF expression in brain regions affected by neurodegenerative processes (Pandey et al., 2021; He et al., 2023). Similarly, Cymbopogon citratus essential oil, dominated by the acyclic monoterpene aldehyde citral (65–85%), similarly enhances BDNF expression to support neuronal resilience and synaptic function (Majewska et al., 2019; Brimson et al., 2021).

Beyond neurotrophic factor modulation, essential oils engage specific receptor systems that regulate neuronal excitability and inflammatory responses. GABAergic receptor modulation represents a mechanism recurrently observed across multiple EOs despite distinct phytochemical compositions. Lavender (Lavandula angustifolia) essential oil demonstrated neuroprotective effects in scopolamine-induced dementia rat models through combined antioxidant and antiapoptotic mechanisms. The primary constituents linalool (20–35%) and linalyl acetate (30–55%) confer cognitive-enhancing properties through GABAergic modulation, reducing neuronal excitability and potentially preventing excitotoxicity (Prashar et al., 2004; Hancianu et al., 2013). Similarly, Melissa officinalis essential oil, rich in citral (35–45%), and Salvia sclarea essential oil, containing linalool (20–36%) and linalyl acetate (16–36%), demonstrate GABAergic modulatory properties through their predominant monoterpene constituents (Sharafzadeh et al., 2011; Świąder et al., 2019; Doukani et al., 2021). Commiphora myrrha essential oil exerts GABAergic effects through the sesquiterpene lindestrene, indicating that both monoterpene and sesquiterpene structural classes can effectively engage GABA receptor systems (Alsuwayt and Chidrawar, 2021).

Cannabinoid receptor type 2 (CB2) activation represents an additional receptor-mediated neuroprotective mechanism distinct from classical neurotransmitter systems. Essential oils containing the sesquiterpene β-caryophyllene, including Boswellia carterii and Syzygium aromaticum, activate CB2 receptors (Gaara et al., 2007; Al-Yasiry and Kiczorowska, 2016). β-Caryophyllene functions as a selective CB2 agonist, activating this receptor without engaging CB1 receptors responsible for psychoactive effects, thereby providing targeted immunomodulatory effects relevant to neuroinflammation (Aly et al., 2019). CB2 receptor activation on microglia suppresses pro-inflammatory phenotype polarization, reducing production of inflammatory mediators including TNF-α, IL-1β, and reactive oxygen species while promoting anti-inflammatory cytokine release (Grabon et al., 2024). This receptor-mediated anti-inflammatory mechanism operates independently of and complementarily to NF-κB pathway inhibition and NLRP3 inflammasome suppression demonstrated by other essential oil constituents.

Therefore, anti-AD efficacy appears achievable through markedly different phytochemical compositions, ranging from monoterpene-dominated oils (Eucalyptus globulus: 70–85% 1,8-cineole; Cymbopogon citratus: 65–85% citral) to sesquiterpene-rich formulations (Pogostemon cablin: 32–40% patchoulol; Zingiber officinale: 30–40% α-zingiberene) to phenylpropanoid-based oils (Syzygium aromaticum: 70–85% eugenol), suggesting chemical diversity may be leveraged for personalized therapeutic approaches based on individual patient tolerability profiles or disease subtypes.

4. Conclusions and future perspectives

This comprehensive review demonstrates that EOs represent a promising class of multi-targeted therapeutic agents for neurological and psychiatric disorders, operating through convergent mechanisms that address the multifactorial pathogenesis underlying these conditions. Across psychiatric disorders, sleep disturbances, and neurodegenerative diseases, EOs consistently modulate critical pathophysiological processes including neurotransmitter system dysregulation, HPA axis hyperactivity, oxidative stress, neuroinflammation, protein aggregation, and neurotrophic factor depletion. The chemical diversity of essential oil constituents—spanning monoterpenes (linalool, α-pinene, limonene, 1,8-cineole), sesquiterpenes (β-caryophyllene, patchoulol), phenylpropanoids (cinnamaldehyde, eugenol), and their oxygenated derivatives—enables engagement of multiple molecular targets through distinct yet complementary mechanisms. Notably, individual EOs demonstrate synergistic interactions wherein specific constituent ratios produce effects exceeding the sum of individual components, supporting the therapeutic rationale for whole oil formulations over isolated compounds. The favorable safety profiles observed in studies, characterized by high therapeutic indices and minimal adverse effects at efficacious doses, position EOs as viable candidates for long-term preventive interventions in at-risk populations or as complementary therapies augmenting conventional pharmacological treatments. The capacity of EOs to simultaneously address multiple pathogenic processes through diverse yet convergent mechanisms represents a paradigm shift from single-target pharmaceutical approaches toward multi-targeted, systems-level interventions more appropriately matched to the complex, multifactorial nature of neurological and psychiatric disorders. As scientific understanding of essential oil pharmacology deepens and clinical evidence accumulates, these natural compounds hold substantial promise for expanding the therapeutic armamentarium against neurological diseases.

Despite the considerable promise demonstrated by EOs in neu-

rological applications, several important limitations of current research warrant careful consideration. First, the majority of mechanistic studies have been conducted in vitro or in animal models, with a notable paucity of large-scale, randomized controlled clinical trials in human populations. The extrapolation of findings from rodent models to human neurological disorders remains challenging due to inherent species differences in blood-brain barrier permeability, metabolic pathways, and receptor expression patterns. Second, substantial variability exists in EOs chemical composition depending on plant species, geographical origin, cultivation conditions, extraction methods, and storage conditions, which complicates standardization efforts and reproducibility across studies. The lack of standardized analytical protocols for compositional characterization and quality control represents a significant barrier to clinical translation. Third, the pharmacokinetic properties of EOs remain inadequately characterized in humans, particularly regarding central nervous system penetration, regional brain distribution, and the identification of active metabolites. Fourth, optimal dosing regimens, administration routes (inhalation versus oral versus transdermal), treatment durations, and potential long-term safety concerns require systematic investigation through clinical studies. The potential for drug-essential oil interactions, particularly in polypharmacy scenarios common among elderly populations with neurodegenerative diseases, necessitates comprehensive assessment.

In conclusion, despite the identified limitations of current research, EOs demonstrate substantial therapeutic potential for neurological and psychiatric disorders through their multi-targeted mechanisms and favorable safety profiles. The convergence of diverse phytochemical compositions on common therapeutic targets—including neurotransmitter systems, neuroendocrine pathways, and neuroprotective mechanisms—supports their investigation as complementary therapeutic strategies. Future research priorities must focus on rigorous clinical trials with standardized preparations, comprehensive pharmacokinetic characterization, and advanced mechanistic studies to fully realize the clinical potential of these natural compounds. As the field advances through these concerted efforts, EOs hold promise for expanding treatment options and improving patient outcomes in neurological medicine.

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Conflict of interest

The authors declare no conflict of interest.

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