Mechanisms of Essential oils on Central Nervous System

Subjects: Neurosciences

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Essential oils (EOs) are naturally occurring complex mixtures of volatile odor compounds synthesized as secondary metabolites by plants and are extracted through steam distillation, solvent extraction, maceration, cold press extraction, water distillation, and CO2 extraction. Novel methods that are more efficient and provide higher yields include supercritical fluid extraction, microwave-assisted extraction, and ultrasound. Studies conducted on animals and humans have shown that EOs can produce a variety of central nervous system (CNS) targeted pharmacological effects such as anxiolytic effect, neuroprotection, antidepressant effect, anticonvulsant effect, analgesic, and sedative effect, to name a few. As a result, EOs can be used as an adjuvant therapy to prevent and relieve symptoms associated with CNS-based disorders such as insomnia, depression, dementia, Alzheimer's disease (AD), etc.

essential oils aromatherapy Alzheimer's disease Parkinson's disease Depression

1. Role in Pain Management

About 84% of old patients suffer chronic pain that is undiagnosable, persistent, and complex. This further leads to a reduction in the quality of life coupled with anxiety and poor sleep. Moreover, 70–85% of the geriatric population suffers from chronic back pain. With respect to women, 25–97% suffer from menstrual pain, while 15% of the female population suffer from severe pain causing impairment in day-to-day activities [1].

According to a review paper by Yang et al., the parts of the brain associated with pain perception include the primary somatosensory cortex, secondary somatosensory cortex, anterior cingulate cortex (ACC), prefrontal cortex (PFC), insular cortex, amygdala, thalamus, cerebellum, and periaqueductal gray (PAG) [2]. Therefore, researchers hypothesized that the analgesic effects associated with certain EOs could be attributed to targeting certain regions of the brain. The constituents that possess analgesic activity, as well as their mechanism of action, are discussed below.

1.1 Clove Oil

The analgesic and anti-inflammatory effect of clove oil, especially for toothaches, is well documented. The main constituent of clove oil is eugenol, which is highly therapeutic [3][4]. Studies conducted by Chung et al. [5] show that the analgesic effects of eugenol occur through the inhibition of voltage-gated sodium (Na^+) and Ca(V) 2.2, 2.3 calcium (Ca^{2+}) channels and currents without the involvement of transient receptor potential cation channel

vanilloid 1 (TRPV1). Eugenol also causes the inhibition of pro-inflammatory mediators such as lipoxygenase, interleukin 1β, cyclo-oxygenase, and nitric oxide synthase [6]. Studies conducted by Xu et al. determined that TRPV3, which is a heat sensitive Ca^{2+} permeable ion channel in the skin, tongue, and nose, is expressed by eugenol [7].

Following the entry into the bloodstream, either through inhalation or massage therapy, the analgesic activity of eugenol on the CNS is attributed to the ability of eugenol to potentiate the $GABA_A$, receptors thereby increasing the affinity of GABA to the receptors, a mechanism observed in benzodiazepines and barbiturates [8][4][9]. Moreover, studies conducted by Bo et al. suggested that eugenol can modulate glutamatergic receptors and inhibits TNF-α [10].

In addition to being analgesic, eugenol is also associated with antioxidant and antidepressant activity, as confirmed by Dhiman et al. [11], who designed and synthesized eugenol-based derivatives, performed in vitro, in silico studies, and tested their MAO (A and B) inhibitory activity as agents for neurological disorders. Radical scavenging activity was also determined using H_2O_2 and DPPH scavenging methods followed by spectrophotometric titrations. All the synthesized compounds showed significant MAO inhibition through interaction with the MAO active site, as observed through molecular docking studies. Two synthesized compounds showed activity hMAO-A inhibition with IC_{50} values of 5.989 ± 0.007 μM and 7.348 ± 0.027 μM with a selectivity index of 0.19 and 0.14, respectively, while two other synthesized compounds showed hMAO-B inhibitory activity with IC_{50} values of 7.494 ± 0.014 μM and 9.183 ± 0.034 μM with a selectivity index of 5.14 and 5.72, respectively, indicating their potential antioxidant activity in antidepressant therapy and neurological disorders [11].

1.2 Lavender Oil

Due to many bio-active constituents, lavender oil can be used for various functions. According to studies conducted by Pinto et al., the analgesic effect of (-) linalool is attributed to the inhibition of the release of substance P or through antagonistic action on its receptor neurokinin-1 (NK-1) [12]. Moreover, (-) linalool also can cause inhibition of the active field potentials that occur through the antidromic stimulation of the hylus, indicating its ability to activate the voltage-gated Na^+ channels in the granular neurons of the hippocampal dentate gyrus [13][14]. It also can modulate neurogenic and inflammatory pain through a reduction in peripheral and central nerve excitability [13]. (-) Linalool is also reported to cause a significant decrease in carrageenin-induced edema and acetic acid-induced writhing. This effect was diminished in the presence of atropine, a muscarinic receptor antagonist, and by naloxone, an opioid receptor antagonist indicating its cholinergic activity. Studies conducted by Peana et al. agree with the demonstrated pharmacological properties of linalool. They confirmed its ability to act as a cholinergic, local anesthetic and causes blockage of NMDA receptors. They also suggested that a key role in its activity is related to the opening of potassium ($K^{+)}$ channels, which possibly occurs due to the stimulation of muscarinic M2, opioid, or dopamine D2 receptors [15][16]. Research conducted by Tashiro et al. on orexin neuron-deficient and orexin peptide-deficient mice subjected to formalin tests showed that orexinergic transmission was essential for linalool odor-induced analgesia, indicating that linalool caused the activation of hypothalamic orexin neurons, which act as critical mediators for processing pain [17]. Other studies conducted indicated that lavender oil was also found to

bring about a decrease in ERK1, ERK2, and JNK1 phosphorylation along with iNOS level reduction. Moreover, lavender oil was also found to inhibit the degradation of FAAH (fatty acid amide hydrolase) and MAGL (monoacylglycerol lipase), thereby causing significant antinociception through the elevation of endocannabinoid levels in neuropathic pain models. These enzymes are essential for the synthesis and degradation of endocannabinoids as per the requirements of the body. Inhibition of FAAH and MAGL degradation causes the upregulation of AEA (anandamide) that has been found to be involved in emotion regulation. **Figure 1** illustrates the process by which lavender oil exerts its effects on the endocannabinoid system (ECS) [18].

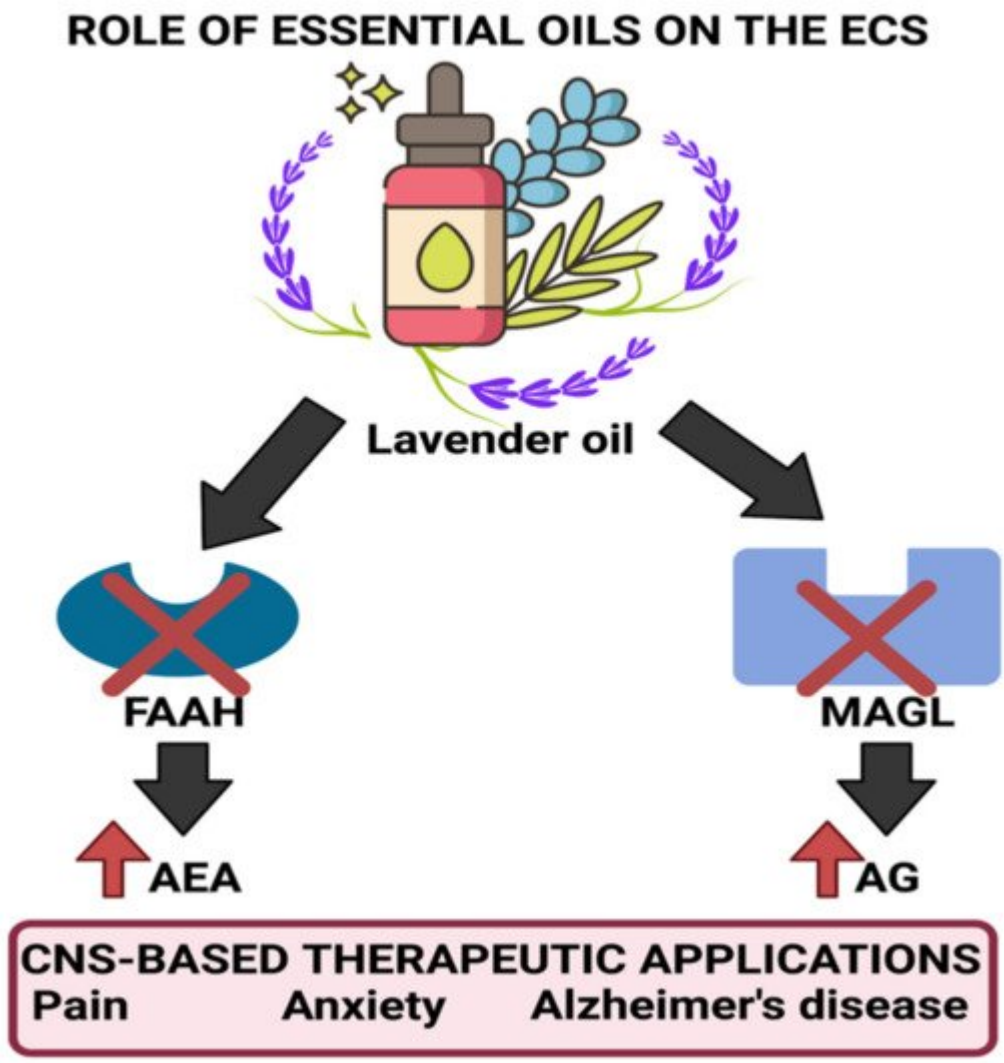

Figure 1. Ability of lavender oil to inhibit the degradation of FAAH and MAGL, thereby increasing levels of AEA and AG, which assist in mood elevation and analgesic effects. Created using Biorender.com. (Last accessed on 14 December 2021).

2. Role in Anxiety Relief and Stress Management

Anxiety disorders are the most common mental disorders in the United States, affecting approximately 40 million people aged 18 or older. They occur due to many reasons, such as genetics, life events, personality, and brain

chemistry. Although treatable, only 36.9% of the population receive treatment. Anxiety disorders include generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder, obsessive-compulsive disorder (OCD), stress, post-traumatic stress disorder (PTSD), major depressive disorder, and persistent depressive disorder (PDD) [19]. The current primary treatments for anxiety include psychotherapy such as cognitive-behavioral therapy (CBT), antidepressant drugs, and anti-anxiety medication such as buspirone, benzodiazepines, and ß-blockers, which are associated with a lot of side effects [20]. The essential oils that can be used for anxiety relief and stress reduction include:

2.1 Frankincense oil

The essential oil of Frankincense contains 147 compounds that attribute to its activity, such as α-pinene, β-pinene, α-thujene, myrcene, sabinene, limonene, para cymene, and β-caryophyllene [21]. An animal model-based study conducted in 2019 by Okano et al. indicated a significant reduction in the levels of stress marker corticosterone and the endogenous antioxidant glutathione when administered in the undiluted and diluted form (1:1000) with jojoba oil, thus indicating the attenuation of induced stress by the essential oil of Frankincense. A decline in non-rapid eye movement and enhancement of wakefulness time was also observed after administering the diluted form. However, upon isolation of significant components, α-pinene and limonene from the oil, a decline in corticosterone levels was not observed, indicating that the constituents of the essential oil work synergistically to produce the anxiolytic effect [22].

2.2 Lavender oil

As mentioned earlier, the major constituents of lavender oil are believed to exert their effects through interactions with the GABAergic system [23]. Concerning anxiety relief and stress management, a study conducted in 2005 indicated a decline in anxiety, stress, and improved mood following inhalation of the scent of lavender oil [24]. Moreover, a 2012 study on postpartum women indicated that aromatherapy using lavender oil for 15 min twice a week for four weeks lowered anxiety levels and caused a decline in depression levels [25]. In 2015, an improvement in sleep, energy, and vibrancy was noted in students who suffered from sleep deprivation and inhaled the scent of lavender oil before bedtime [26]. Another research group also observed this sleep-promoting effect in 2015 [27]. In 2018, geriatric populations with enhanced duration and sleep quality followed aromatherapy involving lavender oil [28]. Taken together, these studies further confirm the exertion of the oil's anxiolytic effect through interactions with the GABAergic system.

2.3 Lemongrass oil

The major constituents of the oil are citral (a mixture of niral and geranial) and β-myrcene [29][30]. An animal model study conducted in 2011 determined that the anxiolytic activity of lemongrass oil at a dose of 10 mg/kg (p.o) possibly occurs through interaction with the GABA receptor–benzodiazepine complex as the effect of lemongrass oil was inhibited by flumazenil, a competitive antagonist of benzodiazepines [31][32]. Moreover, in a study conducted in 2015, the aroma of lemongrass (from three to six drops) brought about a significant decline in stress and anxiety

in subjects [33]. Similar to lavender oil, lemongrass oil is believed to exert its effect through interactions with the GABAergic system [29].

3. Role in Depression Management

According to the NIH, depression is a prevalent mental disorder and can occur due to genetic, biological, environmental, and psychological factors or a combination of these factors. Treatments include a form of psychotherapy such as electroconvulsive therapy (ECT) and antidepressants [34]. The complications associated with depression include weight gain, social isolation, self-mutilation, pain, alcohol and drug abuse [35]. Essential oils that can use for mood improvement and symptom alleviation of depression include:

3.1 Ylang ylang oil

This essential oil consists of approximately 150 identified compounds. However, the mood adjustment and relaxation effect provided have been attributed to β-caryophyllene, benzyl benzoate, linalool, and benzyl alcohol in the oil [36][37]. In 2013, the impact of ylang-ylang EO was studied on 15 healthy men wherein three drops of the oil were added to a warm water lamp maintained at 90 °C in an enclosed space. After 60 min of exposure, the subjects' heart rate and blood pressure levels decreased along with a simultaneous decline in the activation of the autonomic nervous system (ANS) [38]. In 2018, a study showed that inhalation of ylang ylang essential oil by anxious mice caused a decline in CREB and Fos-c in the hippocampus, decreased plasma corticosterone, and altered blood serotonin metabolism [39]. In 2016, the mechanism behind the anxiolytic and mood adjusting effect was identified to occur through effects on the serotoninergic (5-HT) and dopaminergic pathways (DA) and was attributed to the presence of benzyl benzoate in the oil [37]. Moreover, its major constituent, β-caryophyllene, is also associated with anti-inflammatory, anticancer, neuroprotective, antioxidant, and mood-adjusting effects [40][41][42]. Studies have indicated that the mood adjusting effects of ylang ylang oil occur due to the direct binding of β-caryophyllene to CB2R receptors located on several organs, which cause the modulation of ECS activity, thereby controlling responses (both cognitive and emotional) to stressors through ECS interactions [43]. The ability of β-caryophyllene to modulate various pathways and possess multiple benefits through the CB2R receptor has been illustrated in **Figure 2**. β-caryophyllene has been found to hinder metastasis, cause a reduction in oncogene and protein expression of cancer cells while upregulating genes and proteins that destroy cancer cells through the modulation of pathways such as MAPK, PI3K, AKT, mTOR, S6K1, and STAT3. Therefore, its use is suggested for kidney, lung, oral, liver, lymphoma, and neuroblastoma cancers due to its chemo preventive activity [18]. β-caryophyllene when administered orally, has been found to inhibit CD14/TLR4/MD2 toll-like receptor complex that is responsible for the production of pro-inflammatory cytokines, such as IL-1β, IL-8, IL-6, and TNF-α, while also causing the synergy of μ-opioid receptor pathways [44][45]. Moreover, it has also been attributed to modulating pain signaling pathways in a synergistic manner with other analgesic substances [46]. **Figure 2** illustrates the various pathways affected through interaction with the ECS.

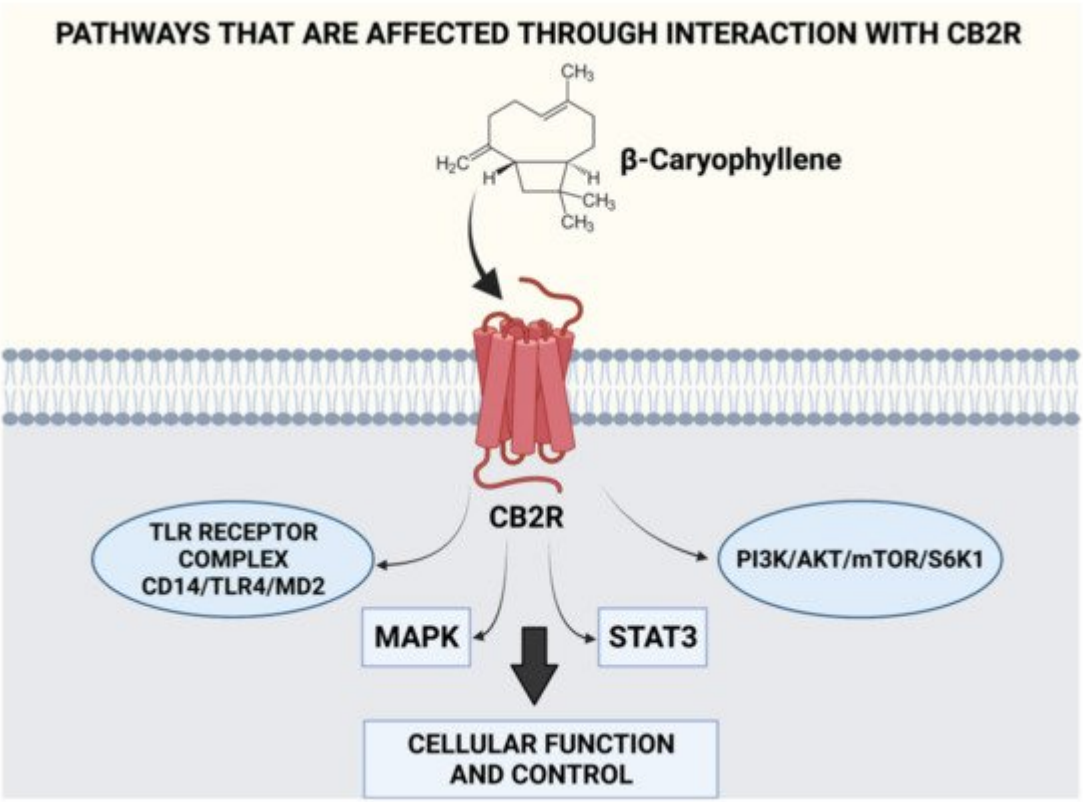

Figure 2. Interaction of EOs with the ECS leads to the modulation of several pathways. Created using Biorender.com. (Last accessed on 14 December 2021).

3.2 Cinnamon oil

The oil consists of 15 identified compounds, and the principal component (65–85%) is trans-cinnamaldehyde which is responsible for the mood adjustment effect of the oil. Antidepressant effects in albino male mice were observed following intraperitoneal (i.p) injection (3 in 24 h/1 per day for 14 days) using doses of 0.5, 1, and 2 mg/kg [47]. The mechanism of this effect remains unknown. However, in 2016, another group of researchers suggested the downregulation of nitric oxide synthase, cyclo-oxygenase 2 (COX-2), and TNF-α, and suppressing neuroinflammation and NF-κB and p53 in activated B-cells was responsible for the antidepressant effect observed [48]. In contrast, Iwasaki et al. (2008) showed that intravenous (IV) administration of TCAs caused an upregulation of adrenaline secretion through adrenal sympathetic nerves along with the activation of sensory nerves that express thermosensitive transient receptor potential channels A1, thus being beneficial in monoamine-associated depressive disorders where a decline in adrenaline level is observed [49]. Therefore, further research to determine the mechanism by which cinnamon oil exerts its antidepressant effect is needed.

4. Role in Memory Retention, Neuroprotection, and Alzheimer's Disease Management

Disruption of daily life due to memory loss could be an early sign of dementia or Alzheimer's disease. Patients diagnosed with Alzheimer's find it difficult to perform daily tasks and lose track of dates, seasons, important events,

and time. Due to progressive memory loss that occurs over time, patients find it difficult to remember. Causes of Alzheimer's disease are poorly understood. The disease is associated with the presence of amyloid plaques, neurofibrillary tangles, and loss of neural connections in the brain [50][51]. Several EOs have been found to be beneficial for symptom reduction and disease treatment of Alzheimer's disease through various mechanisms such as acetylcholinesterase inhibition illustrated in **Figure 3**, nicotinic/$GABA_A$ receptor interactions, etc. These EOs and the mechanisms by which they cause Alzheimer's disease symptom alleviation are discussed below:

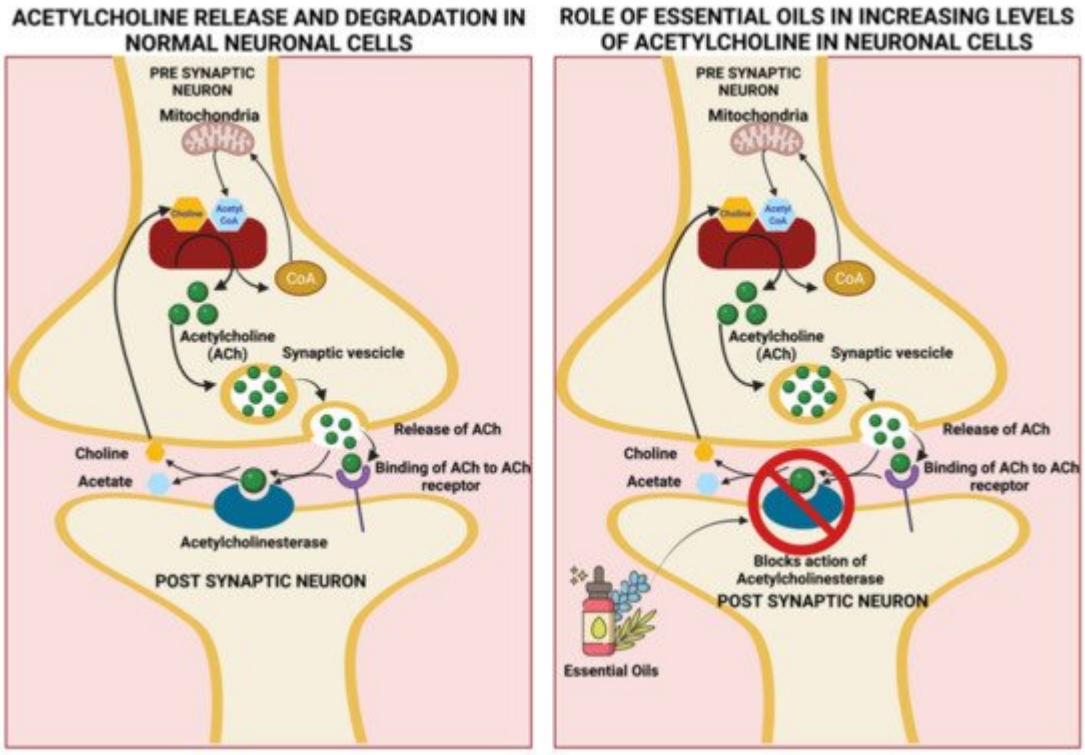

Figure 3. Ability of EOs to inhibit acetylcholinesterase (AChE), thereby increasing levels and duration of acetylcholine in the brain and assisting with memory retention. Created using Biorender.com. (Last accessed on 14 December 2021).

4.1 Eucalyptus oil

The leaves' major constituents responsible for its CNS activities are 1,8-cineole (Eucalyptol) and α-pinene [52]. Eucalyptol is a monoterpenoid, is the major component (90%) of eucalyptus oil, and is well known to provide an anti-inflammatory, mucolytic, and spasmolytic effect on the respiratory tract, thus aiding to relieve inflammatory diseases such as asthma and chronic obstructive pulmonary disease (COPD) [53]. Another component of eucalyptus oil is α-pinene, which exists as a racemic mixture. Besides exerting anti-inflammatory [54] and antimicrobial effects [55], it exerts an inhibitory effect on acetylcholinesterase (AChEI), the enzyme responsible for the breakdown of the neurotransmitter acetylcholine into choline and acetate [56], the results of which leads to enhanced levels and duration of acetylcholine in the CNS, thereby aiding memory as shown in **Figure 3** [54]. The acetylcholinesterase inhibitory effect and mechanism of action of α-pinene is therefore beneficial for the prevention and progression of neurodegenerative disease such as Alzheimer's disease, which is associated with a decline in

levels of acetylcholine due to cholinergic neuron deterioration, which results in memory loss-an important characteristic of the neurodegenerative disease [57].

4.2 Peppermint oil

The oil contains 26 identified volatile compounds, most of which are oxygenated monoterpenes such as menthol and iso-menthone [29][58]. Others include limonene, cineole, menthofuran, menthyl acetate, isoeugenol, pulegone, and carvone [59]. Umezu et al., in 2012, determined the CNS stimulant activity of peppermint oil using a discrete shuttle-type conditioned avoidance task in mice [60]. Similarly, a study conducted by Kennedy et al. in 2018 indicated that the improvement in mood effects and cognitive tasks and decline in mental fatigue in individuals administered with 100 µL of peppermint oil occur through nicotinic/$GABA_A$ receptor binding and acetylcholinesterase inhibition (**Figure 3**) [61]. It also possesses an antioxidant effect, increases glutathione, and prevents oxidative stress. When administered at a lower dose (100 mg/kg s.c), improvement in spatial working memory was observed in mice, while at a higher dose, a decline of malondialdehyde (a lipid peroxidation product) occurs in aged and ß-amyloid treated mice, thus improving cognitive function. When administered in mice for ten days, an improvement in spatial learning and memory along with the reversal of amnesia upon treatment with ß-amyloid was observed, proving its benefits in preventing Alzheimer's disease and memory [62].

4.3 Rosemary oil

The oil contains more than 16 identified compounds, majorly being camphor, cineole, α-pinene, camphene, and α-terpineol [29][63]. Besides possessing anxiolytic properties, rosemary oil also aids in memory, mood, and cognitive functions. In 2017, the inhalation of rosemary oil by mice increased dopamine levels while decreasing immobility time and serum corticosterone levels. The mechanism behind the effects occurred through intracellular modulation of acetylcholine, choline, and Gap43 gene expression levels. Moreover, rosemary oil was found to affect the stress response system through the nerve growth factor (NGF) pathway and the hypothalamus–pituitary–adrenal axis, thus bringing about dopamine activation (DAergic system activation) secretion. The authors attributed this effect to α-pinene, a known anxiolytic [64]. Rosemary oil also offers antioxidant-mediated neuronal protection against brain inflammation and ß-amyloid plaques observed in Alzheimer's disease [65].

4.4 Sage oil

Sage oil contains camphor, α-thujone, 1–8, cineole, viridiflorol, β-thujone, β-caryophyllene, and 49 other constituents [29][66]. A study conducted in 2014 showed that sage oil could modulate retrospective memory, attention, and mood [67] by acting as an acetylcholinesterase inhibitor. Sage oil also acts as a powerful antioxidant, enhances antioxidant defense systems, and prevents lipid oxidation, beneficial for induced acquisition and memory deficits observed in diabetic patients [68]. Moreover, it has shown beneficial effects on patients with mild to moderate Alzheimer's disease. After four months of usage of sage oil (fixed dosage 60 drops/day), patients showed improved cognitive function [69].

4.5 Sandalwood oil

Sandalwood oil consists mainly of tricyclic α-santalol and β-santalol [70]. A study conducted in 2020 by Younis et al. showed that sandalwood essential oil improved neurological deficits decreased oxidative stress and inflammatory cascade in mice subjected to middle cerebral artery occlusion surgery (MCAO) [71]. The methanolic extracts of sandalwood administered to albino mice showed acetylcholinesterase inhibitory effect along with α, α-diphenyl-β-picrylhydrazyl (DPPH) superoxide radical free scavenging activities, thus proving beneficial to prevent the progression of dementia and loss of memory in Alzheimer's patients [72][73]. A 2016 study on 32 humans showed a reduction in blood pressure and salivary cortisol levels, indicating its benefits in stress reduction as well [74].

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