Effects of essential oils on central nervous system: Focus on mental health

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Essential oils have been used as remedies since ancient times for the treatment of numerous illnesses on account of their wide range of biological activities. Recent preclinical and clinical studies have shown varying pharmacological responses in the nervous system leading to anxiolytic, antidepressant, sedative, and anticonvulsant effects. Experimentation in animal models has evidenced the involvement of multiple neurotransmitter systems in the mode of action of essential oils, resulting in measurable physiological effects in the brain. Additionally, clinical trials have demonstrated the influence of essential oils in physiological parameters such as blood pressure, heart rate, respiratory rate, brain waves composition, and cortisol serum levels with concomitant psychological effects. Although there is growing evidence of measurable effects of essential oils in animal brains, more clinical research is required to validate their influence in the human central nervous system. This will enable the development of essential oil-based drugs for the treatment of mental illnesses such as depression, anxiety and dementia.

KEYWORDS
clinical trials, essential oils, molecular pathways, nervous system, neuropharmacology

1 | INTRODUCTION

Essential oils (EOs) have been recognized as therapeutic agents since ancient times for their wide range of pharmacological and psychological properties. They are a complex mixture of volatile odor compounds mainly consisting of benzenoids, phenylpropanoids, monoterpenoids, and sesquiterpenoids. Historical records show that EOs were already in use more than 2000 years ago in ancient Egypt, India, Persia, Mesopotamia, and China to prevent illnesses, for the treatment of diseases and in religious ceremonies on account of their pleasant odors (Djilani & Dicko, 2012; Kubeczka, 2015; Vergis, Gokulakrishnan, Agarwal, & Kumar, 2015;). EOs have drawn attention from scientists, practitioners, and therapists for their biological activities such as antibacterial, antifungal, antiviral, anti-inflammatory,
antioxidant, anticancer, and antinociceptive properties (Hüsnü Can Başer & Buchbauer, 2016). Human and animal studies have shown that several EOs produce diverse pharmacological responses in the nervous system resulting in anxiolytic, analgesic, antidepressant, anti-convulsant and sedative effects. Therefore, it has been suggested that EOs could be effective for mitigating the symptoms of various mental illnesses including depression, anxiety and dementia. The use of EOs in complementary therapies such as aromatherapy is popular in many countries and involves the administration of EOs by inhalation, skin absorption, or ingestion for prophylactic medical care or active treatment. Nowadays, aromatherapy is used worldwide to alleviate insomnia, depression, anxiety and some cognitive disorders. In the last 10 years, accumulating evidence has shown that the administration of EOs exerts measurable pharmacological effects and when used at an appropriate concentration, seems to be safe without showing adverse effects, which are common in several commercial psychotropic drugs. However, more scientific evidence is required to prove their pharmacological efficiency in the human nervous system.

Depression and anxiety disorders are the most prevalent mental illnesses with a worldwide prevalence of 4.4% and 3.6%, respectively (WHO, 2017) although these numbers may be an underestimation of their true scale due to the underreporting of cases. The total number of people suffering from depression and anxiety disorders in the world is estimated in 322 and 264 million, respectively. The World Health Organization (WHO) reported that depression is the single largest contributor to global disability (7.5%) whereas anxiety is ranked sixth in the same category (WHO, 2017). It has been shown that depression is the major contributor to suicide, which accounted for 1.5% of all deaths worldwide in 2015, placing it into the top 20 leading causes of death (WHO, 2017). Anxiety disorders are comprised of generalized anxiety, social anxiety disorder, specific phobias, separation anxiety disorder and panic disorder with or without agoraphobia (Bandelow & Michaelis, 2015). The majority of conditions are treated with both pharmacotherapy and psychotherapy. The most frequently recommended first-line medication are both, selective serotonin reuptake inhibitors and selective serotonin norepinephrine reuptake inhibitors, since they have shown a good benefit/risk balance (Thibaut, 2017). However, these treatments are associated with significant side effects which, in some patients, can lead to a suboptimal therapeutic outcome.

Numerous studies suggest that only some of the major compounds of the EOs contribute significantly to their anxiolytic and antidepressant effects including linalool, limonene, and pinene (Figure 1). Hence, EOs with high content of these compounds are expected to have anxiolytic and antidepressant properties (Han, Gibson, Eggett, & Parker, 2017). For at least a decade now, EOs have been gaining popularity as complementary medicines to alleviate depression and anxiety, not only because of their proven pharmacological effects but also to avoid the side effects produced by the chronic use of synthetic anxiolytic and antidepressant drugs (Figure 2). On the one hand, chronic use of anxiolytics such as benzodiazepines (BDZs) induces lethargy, drowsiness, dizziness, vertigo, tolerance, and sedation (Rombolà et al., 2017). Furthermore, BDZs have also been involved with falls and exacerbation of cognitive decline in older adults (Alvarenga, Giacomini, de Loyola Filho, Uchoa, & Firmo, 2014). On the other hand, synthetic antidepressant drugs such as monoamine oxidase inhibitors, tricyclic antidepressants (TCAs), and selective

![Figure 1](image1.png)  
**FIGURE 1** Chemical structure of common active compounds in essential oils with neural activities

![Figure 2](image2.png)  
**FIGURE 2** Chemical structure of common commercially available drugs with antidepressive, anxiolytic and sedative properties
serotonin reuptake inhibitors (SSRIs) can produce weight gain, fatigue, sexual dysfunction, headache, sedation, constipation, and tachycardia (Figure 2) (Santarsieri & Schwartz, 2015). For these reasons, there is an increasing demand and interest of alternative medicines to treat depression and anxiety with reduced or no side effects. Additionally, psychostimulant EOs have been shown to interact with ascending neurotransmitter systems that are involved in the alert waking state. It has been shown that induction of the alert waking state along with concomitant activation of the forebrain depends upon a range of ascending neurotransmitter systems including the serotonergic, cholinergic, noradrenergic, and histaminergic (Rombló et al., 2009).

A variety of EOs have been shown to have free radical scavenging and antioxidant properties that confer neuroprotective effects which can improve cognitive function and reduce brain damage. Cognitive function in this context, refers to various mental abilities including memory, reasoning, planning, decision-making, attention span, speech, language, and judgment (Alzheimer’s Association, 2016; Fisher et al., 2019). The deterioration of cholinergic neurons has been shown to lead to cognitive deficits, especially in the case of degenerative diseases. Dementia is considered a major neurocognitive disorder affecting cognitive function and therefore the performance of everyday activities. Simple everyday activities such as making a meal, shopping, paying bills, etc. can become a challenge for people suffering from dementia. Alzheimer’s disease (AD) is the most common cause of dementia, accounting for 60%-80% of cases (Alzheimer’s Association, 2016). In 2016, 5.4 million Americans were estimated to have AD and it was the sixth leading cause of death in the United States. In Europe, the prevalence of AD was estimated at 5.05% in 2017, affecting 3.31% of men and 7.13% of women. Globally, the trend of Alzheimer’s prevalence is increasing together with the increase of elderly population (Niu, Álvarez-Álvarez, Guillén-Grima, & Aguinaga-Ontoso, 2017). Varying EOs have shown anticholinesterase activity, which might be advantageous for the development of drugs for AD treatment since cholinesterases have been recognized as one of its potential targets (Das & Pandima Devi, 2018).

A large body of research confirms measurable physiological effects of EOs in humans through a variety of parameters such as blood pressure (BP); heart rate (HR), and respiratory rate (RR); alpha and beta brain waves; and corticosteroid serum levels. Additionally, a variety of behavioral perception tests have been performed in humans, which have also evidenced the psychological effects of EOs. Furthermore, similarly to conventional psychotropic drugs, EOs have shown to interact with a range of neurotransmitter circuits in several animal models including noradrenergic, serotonergic, GABAergic and DAergic systems.

This review summarizes relevant studies on both the neuropharmacology and molecular mechanisms that are involved in the neurological effects of EOs were analyzed and revised. Preclinical studies and clinical trials within the period 2004–2019 were included. Literature was collected by examining a range of scientific databases like PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Google Scholar (http://www.scholar.google.co.in), Elsevier (https://www.elsevier.com/en-in), Science Direct (http://www.sciencedirect.com), Wiley (http://www.onlinelibrary.wiley.com), Springer Link (http://www.springer.co.in), and Scopus (http://www.scopus.com). Additionally, information was examined from recognized books, conference proceedings and nonimpact journals. Also, several articles were found by accessing the journal websites or by tracking citations from other publications. The search of the different plants was performed by using the keywords Boswellia sp, Frankincense essential oil, Cananga odorata, Ylang Ylang essential oil, Cinnamomum verum, Cinnamon essential oil, Citrus aurantium, Neroli essential oil, Citrus bergamia, Bergamot essential oil, Citrus sinensis, Sweet orange essential oil, Cymbopogon citratus, Lemongrass essential oil, Lavandula angustifolia, Lavender essential oil, Citrus paradisi, Grapefruit essential oil, Pelargonium graveolens, Geranium essential oil, Rosa damascena, Rose essential oil, Rosmarinus officinalis, Rosemary essential oil, Salvia scarea, Clary sage essential oil, Anthemis nobilis, Roman chamomile essential oil, Pogostemon cablin, Patchouli essential oil, Mentha piperita, peppermint essential oil, Salvia officinalis, Sage essential oil, nervous system, animal testing, clinical trials, neuropharmacology, molecular pathways, anxiolytic, and antidepressant effects. The scientific names of the plants were confirmed from The Plant List (http://www.thelwantlist.org/). The collection of literature was restricted to publications in English. Chemical names were authenticated from PubChem website (pubchem.ncbi.nlm.nih.gov) and figures of chemical structures were made using ChemDraw Ultra 12.0.

3 | CHEMICAL COMPOSITION OF EOS

EOs are typically composed of a complex mixture of secondary metabolites produced by aromatic plants. The main chemical groups found in EOs are benzenoids, phenylpropanoids, monoterpenoids, and sesquiterpenoids, from which terpenes are the largest chemical group. The number of compounds in the majority of EOs is in the range of 100–250 whereas in some cases like in lavender, geranium and rosemary can be up to 500. Some chemicals may be dominant and represent more than 90% of the EO composition such as A-caryophyllene or limonene. The most common compounds found in EOs are linalool, linalool, and pinene (Figure 1; De Groot & Schmidt, 2016).

EO chemical composition can vary significantly depending on multiple factors including the conditions of the aromatic part of the
plant, the geographical location, the extraction method and the extraction time. Also, the drying method of botanicals has been shown to have a significant effect in oil yield and composition (Omidbaig, Hassani, & Sefidkon, 2003). Furthermore, there can be significant differences among chemotypes of a particular botanical.

Varying extraction methods are used to produce EOs including steam distillation, dry distillation, hydro-distillation and high-pressure steam distillation. Cold pressing is used in the case of peel oil extraction specifically from citrus fruits. Steam distillation is the most common method widely used for industrial production of EOs. Although, the application of solvent extraction methods using various solvents (e.g., hypercritical CO2 extraction or supercritical fluid extraction) are gaining popularity in the flavor and aroma industry, the extracts obtained by these techniques are not considered true EOs (Hüsnü Can Başer & Buchbauer, 2016).

4 | ACTIONS OF EOS ON THE CENTRAL NERVOUS SYSTEM

A large body of research confirms the multiple benefits that EOs have on the mental health of humans including anxiolytic/antidepressant effects, cognitive processing enhancement, attention enhancement, psychostimulant effects and memory improvement (Tables 1 and 2). Moreover, varying animal models have been used to elucidate the diverse molecular pathways involved in the therapeutic effects of EOs such as HPA axis, sympathetic nervous system, cAMP response element-binding protein (CREB) signaling pathway and neurotransmitter systems including serotonergic, DAnergic and GABAergic pathways (Figure 3).

In mammals, the hypothalamic–pituitary–adrenal (HPA) axis, the sympathetic nervous system, and the efferent vagus nerve are all responsible for the response of the central nervous system (CNS) to stress. Stressors stimulate the release of the corticotrophin-releasing hormone (CRH) in the paraventricular nucleus (PVN). This is located in the hypothalamus, which stimulates the synthesis and secretion of the adrenocorticotropic hormone (ACTH) by the pituitary gland (Figure 3). ACTH, in turn, induces adrenal synthesis and release of glucocorticoids (cortisol in humans and corticosterone in rodents) in the adrenal glands (Chung, Son, & Kim, 2017; Raison, Capuron, & Miller, 2006). Glucocorticoids along with acetylcholine (ACH), released by the adrenal gland and the efferent vagus nerve respectively, exert anti-inflammatory effects by binding to receptors on cytokine producing cells (e.g., macrophages, T cells, natural killer cells) (Slavich & Irwin, 2014). Moreover, under acute stress or persistent HPA activation, cortisol can increase the reuptake of serotonin by enhancing the synthesis of the serotonin transporter (SERT) (Tafet, Idoyaga-Vargas, Abulafia, & Calandria, 2001). This results in decreased levels of serotonin in the synaptic cleft, which is one of the hallmarks of depression.

Stressors also activate the proinflammatory sympathetic nervous system response with the consequent release of adrenaline (AD) and noradrenaline (NA) from the adrenal gland and sympathetic nerves respectively, increasing both HR and BP (Slavich & Irwin, 2014). Both, adrenaline and noradrenaline activate transcription factors in cytokine producing cells including the nuclear factor kappa-light-chain-enhancer (NF-kB). Subsequently, activation of NF-kB stimulates the transcription and release of proinflammatory cytokines including interleukin 1 (IL-1), interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) (Raison et al., 2006). These cytokines can exert their effects by stimulating the afferent vagus nerve, or by reaching the brain through active molecules and/or by crossing the blood–brain-barrier. The afferent vagus nerve relays information to brain regions involved in mood regulation, sensitivity to social threat, motivation and arousal (Raison et al., 2006; Slavich & Irwin, 2014). Once cytokines reach the brain, they can alter the metabolism of neurotransmitters such as serotonin (5HT) and dopamine (DA), whose dysregulation is intimately associated with depression (Raison et al., 2006). Hence, activation of the proinflammatory cytokines leads to cognitive, emotional and behavioral alteration that can result in anxiety disorders or depression.

EOs have been shown to interact with both the anti-inflammatory and proinflammatory responses of the CNS to stress. For example, frankincense (Okano, Honda, Kodama, & Kimura, 2019), ylang-ylang (Jung, Cha, Kim, Ko, & Jee, 2013), neroli (Choi, Kang, Lee, & Seol, 2014) and bergamot (Saiyudthong & Marsden, 2011), sweet orange (Jaafarzadeh, Arman, & Pour, 2013), geranium (Rashidi Fakari, Tabatabaei Chehr, Kamali, Rashidi Fakari, & Naseri, 2015), rose (Hongratanaworakitat, 2009) EOs can affect HPA axis by decreasing glucocorticoid levels producing a calming effect. On the other hand, the proinflammatory response may be suppressed by downregulating NF-kB as in the case of cinnamon EO, resulting in an anxiolytic effect (Chen et al., 2016). Moreover, calming effects are also produced by increasing serotonin levels while decreasing glucocorticoids like in the case of ylang-ylang EO (Zhang, Zhang, Feng, & Yao, 2016; Zhang, Zhang, Feng, & Yao, 2018). Furthermore, it has been demonstrated experimentally that other EOs like rosemary (Moss, Cook, Wesnes, & Ducket, 2003; Villareal et al., 2017), clary sage (Seol et al., 2010), and roman chamomile (Umez, 2012; Umez, Sano, Hayashi, Yoshikawa, & Shibata, 2017) stimulate the DAnergic system resulting in psychostimulant and cognitive-enhancer effects. Additionally, bergamot (Morrone et al., 2007), lemongrass (Costa et al., 2011) and lavender (Guillmain, Rousseau, & Delaveau, 1989) EOs can exert its anxiolytic effects by activating the GABAergic system.

4.1 | Boswellia sp (frankincense) essential oil

Frankincense EO is made from the resins of the Boswellia genus tree, including B. serrata, B. carteri, B. rivae, B. neglecta, B. papyrifera, B. pijoctae, and B. frereana. Although more than 200 compounds have been identified in frankincense EO the main common constituents found in the commercial species are α-pinene, limonene, α-thujene, myrcene, sabine, and para-cymene (Table 1) (Mertens, Buettner, & Kirchoff, 2009; Okano et al., 2019). In a recent animal study, sleep-deprived adult male rats were treated with frankincense EO to evaluate its anxiolytic properties and its effect in sleep and wakefulness.
| Botanical name of plant source/EO name | Assessment method | Animal model/test subjects | Route of administration | Effective dosage/mode of preparation | Outcome | Effect | Reference |
|---------------------------------------|------------------|-----------------------------|-------------------------|--------------------------------------|---------|--------|-----------|
| *Boswellia* sp (frankincense)         | Physiological parameter measurements | Sleep-deprived adult male Sprague–Dawley rats | Topical administration | 50 μL (1:10⁴) on the nape of neck at hourly intervals for 5 hr | Decreased levels of corticosterone and glutathione Increased wakefulness time and decreased non-rapid eye movement time | Antidepressant/anxiolytic | Okano et al. (2019) |
| *Cananga odorata* (Ylang-ylang)      | Cognitive Drug Research system | 144 healthy volunteers | Olfactory | Four drops (100 μL) for 5 min inhalation with a diffuser | Decreased alertness but increased calmness Impaired and lengthened memory | Antidepressant/anxiolytic | Moss et al. (2008) |
|                                        | Physiological parameter measurements and VAS | 24 healthy volunteers | Olfactory | 1 mL for 20 min inhalation with a diffuser | Increased subjective attentiveness and alertness Decreased BP and HR | Antidepressant/anxiolytic | Hongratanaworakit and Buchbauer (2004) |
|                                        | Physiological parameter measurement and VAS | 40 healthy volunteers | Transdermal application | 1 mL (20% w/w) for 5 min massage on the abdomen, which was subsequently covered with a film for 20 min absorption | Decreased BP and increased skin temperature Increased of calmness and relaxation | Antidepressant/anxiolytic | Hongratanaworakit and Buchbauer (2006) |
|                                        | Physiological parameter measurements | 15 healthy men | Olfactory | Three drops in a warm water lamp for 20 min inhalation | Decreased HR and BP Relief of the arousal level in the autonomic NS | Antidepressant/anxiolytic | Jung et al. (2013) |
|                                        | Physiological parameter measurements and electroencephalography | 10 healthy volunteers | Olfactory | Sniffing for 3 min using an impregnated paper strip | Decreased systolic and diastolic BP Increased alpha brain waves | Antidepressant/anxiolytic | Pujiarti et al. (2012) |
| EPM                                   | Olfactory | Anxious mice | 10 mL EO emulsion (1.0%) for 10 min inhalation with an inhalation apparatus | Altered brain serotonin metabolism | Antidepressant/anxiolytic | Zhang et al. (2018) |
| Botanical name of plant source/EO name. Major and active compounds of EOs | Assessment method | Animal model/test subjects | Route of administration | Effective dosage/ mode of preparation | Outcome | Effect | Reference |
|---|---|---|---|---|---|---|---|
| Cinnamomum verum (cinnamon) TCA | LDB and EPM | Female and male mice | Olfactory | 10 mL EO emulsions (1.0%, 10% v/v) for 10 min inhalation with an inhalator apparatus | Reduced blood plasma corticosterone Increased number of entries and time in the open arms Downregulated cAMP response element-binding protein and c-Fos in the hippocampus | Antidepressant/ anxiolytic | Zhang et al. (2016) |
| Citrus aurantium (Neroli) | FST, TST and EPM | Male albino mice | i.p injection | 2 mg/kg body weight three times in a single day or once daily for 14 days | Decreased immobility time in FST and TST Increased time and entries in the open arms in the EPM | Antidepressant/ anxiolytic | Sohrabi et al. (2017) |
| | FST and multi-box ActiMot detection system | Gerbins | Olfactory | 100 μL vaporized for 30 min-2 h with a nebulizing diffuser | Increased swimming time of gerbils in the FST Locomotor activity did not change | Anxiolytic | Chen et al. (2008) |
| | VAS and MENQOL | 63 healthy postmenopausal women | Olfactory | 1 mL (0.5%) for 5 min inhalation with a fragrance pad twice a day for 5 days | Reduced levels of stress Improved physical conditions Decreased systolic and diastolic BP | Antidepressant/ anxiolytic | Choi et al. (2014) |
| | STAI | 126 woman in labor | Olfactory | 4 mL (0.08 mg/mL) for inhalation every 30 min with gauze squares | Decreased levels of anxiety | Anxiolytic | Namazi et al. (2014) |
| Botanical name of plant source/EO | Assessment method | Animal model/test subjects | Route of administration | Effective dosage/ mode of preparation | Outcome | Effect | Reference |
|---------------------------------|-------------------|-----------------------------|-------------------------|---------------------------------------|---------|-------|-----------|
| Citrus bergamia (bergamot)      | Measurement of release of neurotransmitters | Male Wistar rats | i.p injection and dialysis probe into hippocampus | i.p: 100 μL/kg body weight. Dialysis: 20 μL/20 min (pure or 1:1) | Increased extracellular amino acids neurotransmitters | Antidepressant/ anxiolytic | Morrone et al. (2007) |
| Limonene, linalyl acetate and linalool | Gross behavioral changes and electroencephalography in rats | Male Wistar rats | i.p injection | 500 μL/kg body weight | Increased locomotor and exploratory activities | Increased energy of the faster frequency bands in the EEG spectrum | Antidepressant/ anxiolytic | Rombolà et al. (2009) |
|                                 | EPM and HBT       | Male Wistar rats | Olfactory | Cotton soaked with EO (2.5%) for 7 min inhalation | Increased in percentage of open arm entries and time in the open arms | Increased number of head dips | Attenuated corticosterone response | Antidepressant/ anxiolytic | Saiyudthong and Marsden (2011) |
|                                 | OFT, EPM and FST in rats | Male Wistar rats | i.p injection | 500 μL/kg body weight | Decreased grooming and increased immobility | Increased entries and time in the open arms | | Antidepressant/ anxiolytic | Rombolà et al. (2017) |
|                                 | Measurement of physiological parameters, POMS and STAI tests | 41 healthy women | Olfactory | 400 μL in 400 mL of water for 15 min inhalation with a diffuser | Decreased SC levels | Increased HR Mood improved | Antidepressant/ anxiolytic | Watanabe et al. (2015) |
|                                 | PANAS             | 57 volunteers | Olfactory | 15 min inhalation with a diffuser | Increased positive feelings | | Antidepressant/ anxiolytic | Han et al., 2017 |

(Continues)
| Botanical name of plant source/EO name, Major and active compounds of EOs | Assessment method | Animal model/test subjects | Route of administration | Effective dosage/ mode of preparation | Outcome | Effect | Reference |
|---|---|---|---|---|---|---|---|
| Citrus sinensis (sweet orange), \( \text{d-limonene, } \beta\text{-myrcene, } \alpha\text{-pinene, sabinene, linalool, geranial, and neral} \) | Near-infrared time-resolved spectroscopy and a modified semantic differential approach | Near-infrared time-resolved spectroscopy and a modified semantic differential approach | Near-infrared time-resolved spectroscopy and a modified semantic differential approach | Near-infrared time-resolved spectroscopy and a modified semantic differential approach | Near-infrared time-resolved spectroscopy and a modified semantic differential approach | Near-infrared time-resolved spectroscopy and a modified semantic differential approach | Near-infrared time-resolved spectroscopy and a modified semantic differential approach |
| | STAI and MDBF | Thirty children | Olfactory | 1 hr inhalation with a dispenser | Decreased anxiety | Increased positive mood and calmness | Lehrner et al. (2005) |
| | Measurement of physiological parameters | Fourty men healthy volunteers | Olfactory | 10 drops added to a surgical mask for 5 min inhalation | No change in physiological parameters was detected | Increased positive mood and calmness | Jaafarzadeh et al. (2013) |
| | EPM and the LDB | Male Wintar rats | Olfactory | 400 \( \mu \text{L} \) for 5 min inhalation | Increased time and entries in the lit chamber | Antidepressant/ anxiolytic | Brito Faturi et al. (2010) |
| Cymbopogon citratus (lemongrass), Neral, geranial and \( \beta\text{-myrcene} \) | LDB | Male Swiss mice | Oral administration | 10 mL/kg body weight three times in a single day or once daily for 21 days | Increased time and entries in lit chamber | Antidepressant/ anxiolytic | Costa et al. (2011) |
| | EPM and LDB | Male Swiss mice | Oral administration | 1.0 g/kg body weight for 30 min | Increased time and entries in the lit chamber | Antidepressant/ anxiolytic | Blanco et al. (2009) |
| | Video-monitored version of SCWT, STAI and SPIN | Forty men | Olfactory | Six drops added to a surgical mask for 5 min inhalation | Decreased anxiety and subjective tension | Antidepressant/ anxiolytic | Goes et al. (2015) |
| Botanical name of plant source/EO name, Major and active compounds of EOsa | Assessment method | Animal model/test subjects | Route of administration | Effective dosage/mode of preparation | Outcome | Effect | Reference |
|---|---|---|---|---|---|---|---|
| *Lavandula angustifolia* (lavender) Linalyl acetate, linalool, lavandulyl acetate, myrcene, terpinen-4-ol, −terpineol, cis-linalool oxide, trans-linalool oxide and ocimene | MDAS and STAI-6 | 340 patients | Olfactory | Five drops in 10 mL of water with a candle warmer, twice a day for 4 weeks | Decreased current anxiety | Antidepressant/anxiolytic | Kritsidima et al. (2010) |
| *EPM* Mongolian gerbil | Twelve drops daily for 24 hr inhalation or 14 days with a vaporizer | Increased entries in the open arms | Antidepressant/anxiolytic | Bradley et al. (2007a) |
| PMS scale questionnaire | 40 woman | Three drops in 200 mL of hot water, once a day for 7 days | Decreased anxiety, depressive affect, nervousness, pain, bloating and depressive thoughts | Antidepressant/anxiolytic | UzuncaK and Ayaz Alkaya (2018) |
| Stress assessment questionnaire and BIS | 30 healthy volunteers | Olfactory | Two drops of 2% v/v EO added to a cotton swab placed inside of an oxygen face mask for 5 min inhalation | Decreased stress and BIS values | Antidepressant/anxiolytic | Kim et al. (2011) |
| *HAMA, PSQI, clinical global impressions scale, SF-36 health survey questionnaire, and Zung self-rating anxiety scale* | 221 adults suffering from anxiety disorder | Oral | 80 mg/day for 10 weeks | Improved sleep, mental and physical health | Provided relief for anxiety disorder symptoms | Anxiolytic | Kasper et al. (2010) |
| *Citrus paradisi* (grapefruit) Limonene, R-terpinene, R-pinene | NRS | 361 patients undergoing colonoscopy | Olfactory | 0.30 mL in 70 mL of water with a diffuser | Attenuated abdominal discomfort | Antidepressant/anxiolytic | Hozumi et al. (2017) |
| *Pelargonium graveolens* (geranium) b-citronellol, citronellyl formate, geraniol, 10-epi-g-eudesmol, | STAI | 80 patients with acute myocardial infarction | Olfactory | Three drops of 10% v/v or pure EO added to absorbing patches inside oxygen mask for 20 min inhalation twice a day for 4 days | Reduced anxiety | Antidepressant/anxiolytic | Shirzadegan et al. (2017) |
| Botanical name of plant source/EO name. | Assessment method | Animal model/test subjects | Route of administration | Effective dosage/mode of preparation | Outcome | Effect | Reference |
|----------------------------------------|-------------------|-----------------------------|-------------------------|--------------------------------------|---------|--------|-----------|
| geranyl formate and (l)-linalool         | STAI              | 100 nulliparous women       | Olfactory               | Two drops (2% v/v) onto nonabsorbent pieces of fabric attached to the participant’s collar for 20 min | Reduced anxiety scores and diastolic blood pressure | Antidepressant/anxiolytic | Rashidi Fakari et al. (2015) |
| *Rosa damascena* (rose) 2-phenethyl alcohol, citronellol, geraniol, methyl eugenol and eugenol | PSQI              | 60 patients in coronary care | Olfactory               | Three drops added to a piece of paper towel attached to the side of each patient for 8 hr daily for 3 days | Better quality of sleep | Antidepressant/anxiolytic | Hajibagheri et al. (2014) |
| Measurement of autonomic parameters and rating scales | | Forty healthy volunteers | Transdermal application | 1 mL (20%w/w) for 5 min massage subsequently covered with film during 20 min | Decreased breathing rate, blood oxygen saturation and systolic blood pressure Decreased autonomic arousal | Antidepressant/anxiolytic | Hongratanaworakit (2009) |
| EPM                                    | Male Wistar rats  | Olfactory                   | 1.0% or 5.0% w/w EO for 7 min inhalation using an inhalation apparatus | Increased number of visits and time spent in the open arms | Increased exploration in EPM | Antidepressant/anxiolytic | De Almeida et al. (2004) |
| EPM and LDB                            | Gerbils           | Olfactory                   | 600 μL for 24 hr or daily for 2 weeks using a vaporizer or aroma stone | Increased anxiolytic spatiotemporal and exploratory behavior | | | Bradley et al. (2007b) |
| *Rosmarinus officinalis* (rosemary)    | TST               | Mice                        | Olfactory               | 50 μL or 100 μL impregnated in cotton placed inside a chamber for 14 days | Decreased immobility time of mice in the TST and in serum corticosterone level Increased brain dopamine levels | Antidepressant/anxiolytic | Villareal et al. (2017) |
behavior. Decreased levels of the stress markers corticosterone and glutathione were detected in the sleep-deprived rats when frankincense EO was administrated topically in diluted (1:10³ with jojoba oil) and undiluted preparations. It is worth noting that glutathione is an endogenous antioxidant used as a cerebrospinal fluid marker of cellular stress. Hence, the decrease of these markers showed an attenuating effect by frankincense EO in stress-induced elevations of corticosterone secretion. Moreover, administration of diluted frankincense EO (1:10³) was found to increase wakefulness time and decrease nonrapid eye movement sleep time while relieving sleep debt. Additionally, when the two major compounds of the oil were evaluated in isolation (limonene and α-pinenene) no decrease in plasma corticosterone levels was observed indicating that the anxiolytic effects of frankincense EO might be produced as a result of the synergistic effects of its constituents (Okano et al., 2019).

4.2 | Cananga odorata (Ylang ylang) EO

Ylang ylang EO is extracted from the flower of the tree Cananga odorata mainly via stem distillation (Tan et al., 2015). This EO is extensively used in the fragrance industry, in aromatherapy through inhalation and massaging for relaxation and mood adjusting (Tan et al., 2015; Zhang et al., 2018). In terms of the chemical composition of ylang ylang EO, it consists of approximately 150 molecules of different classes including monoterpenes, sesquiterpenes, aliphatic compounds, phenylpropanoids and nitrogen-containing compounds (Tan et al., 2015). However, only the main constituents benzyl benzoate, linalool and benzyl alcohol have been shown to produce anxiolytic and calming effects (Zhang et al., 2016). Moss, Hewitt, Moss, and Wesnes (2008) studied the impact of ylang Ylang EO on mood and cognition in 144 healthy volunteers using the Cognitive Drug Research computerized assessment system (CDR system). When the subjects’ mood was measured, ylang ylang EO was shown to decrease alertness but increase calmness significantly. The EO was also found to impair and lengthen the memory in the majority of cases (Moss et al., 2008). Conversely, in another human study conducted by Hongratanaworakit and Buchbauer (2004), inhalation of ylang Ylang EO was found to have the effect of significantly increasing subjective attentiveness and alertness by using Visual Analog Scales (VAS). This simultaneously also decreased both BP and pulse rate. The reduced level of arousal in the autonomic nervous system did not lead to a deactivation at the behavioral level, that is, none of the subjects felt more relaxed or drowsy after inhalation. The authors suggested that inhalation of ylang ylang EO may uncouple physiological and behavioral arousal processes. Hence, these opposite findings reported by two different research groups suggest that olfactory processing of odors may have an influence in the subjective evaluation of the psychological effects produced by the oil inhalation. In other words, anatomical variation of the olfactory system, that is unique to each individual, could produce a variable outcome in terms of psychological perception. Subsequently, Hongratanaworakit and Buchbauer (2006) obtained different behavioral effects in humans when they used transdermal absorption of ylang ylang EO as an administration route. In this study, physiological parameters

| TABLE 1 (Continued) |
| Botanical name of plant source/EO name. Major and active compounds of EO | Assessment method | Effective dosage/mode of preparation | Route of administration | Animal model/test subjects | Outcome | Effect | Reference |
| Salvia sclarea | Clary sage | Linalool, α-terpineol, geraniol, acetate derivative of geraniol, and myrcene | FST | 0.1 mL (5% v/v) /100 g body weight | Decreased immobility time | Antidepressant/anxiolytic | Seol et al. (2010) |
| Cananga odorata | Ylang ylang | Benzyl benzoate, linalool, benzyl alcohol | BP and RR | 2 mL (5% v/v) for 60 min inhalation using an aroma pad | Decreased systolic and diastolic blood pressure, decreased respiratory rate | Antidepressant/anxiolytic | Seol et al. (2013) |
| Botanical name of plant source/EO name. Major and active compounds of EOs | Assessment method | Animal model/test subjects | Route of administration | Effective dosage/mode of preparation | Outcome | Effect | Reference |
|---|---|---|---|---|---|---|---|
| **Cananga odorata** (Ylang-ylang) Benzyl benzoate, linalool and benzyl alcohol | Electroencephalography and VAS | 20 healthy volunteers | Olfactory | Not shown | Increased alpha brain waves Reduced amplitude of auditory P300 Decreased level of alertness | Enhancer cognitive processing | Ishiguchi et al. (2008) |
| **Lavandula angustifolia** (lavender) Linalyl acetate, linalool, lavandulyl acetate, myrcene, terpinen-4-ol, terpinol, cis-linalool oxide, trans-linalool oxide and ocimene | Vigilance long-term task | 15 healthy patients | Olfactory | 0.29 mg/L of air for 30 min (air flow = 3.51/min) using a natural volatile delivery system | Reduced information processing resources | Enhancer cognitive processing | Watanabe et al. (2013) |
| **Rosmarinus officinalis** (rosemary) Cineole, camphor, α-pinene, camphene and α-terpineol | Measurement of physiological parameters, Geneva Emotion and Odor Scale and electroencephalography | 20 healthy patients | Olfactory | 10% v/v EO for 20 min using an oxygen pump connected with a respiratory mask (airflow rate = 2 L/min) | Increased BP, HR, and RR More active mood Decreased power of alpha1 and alpha2 waves Increased power of beta wave in the anterior region of the brain. | Psychostimulant | Sayorwan et al. (2013) |
| **Anthemis nobilis** (Roman chamomile) Isobutyl angelate, isoamyl angelate and 2-methylbutyl isobutyrate | Tilting type ambulometer test | Male mice | IP injection | 400, 1,600 or 3,200 mg/kg body weight | Ambulation-promoting effects | Psychostimulant | Umezu et al. (2017) |
| **Pogostemon cablin** (patchouli) Patchoulol, δ-guaiene, α-guaiene, α-gurjunene, seychellene, viridiflorol, β-caryophyllene and β-patchouliene | Measurement of physiological parameters and electroencephalography | Healthy patients | Olfactory | Three minutes sniffing using an impregnated paper strip | Increased systolic and diastolic BP Increased alpha wave | Psychostimulant | Pujiarti et al. (2012) |

(Continues)
and self-evaluation of 40 healthy volunteers were recorded before and after transdermal application of the oil. Ylang ylang EO application produced a significant decrease of BP and increase in skin temperature. Additionally, self-evaluation (as assessed using VAS) resulted in increased calmness and relaxation after treatment (Hongratanaworakit & Buchbauer, 2006). In a similar study, Jung et al. (2013) investigated the effect of ylang ylang EO in 15 healthy men. Three drops of the oil were added to a 90°C warm water lamp, which was placed in a room with the doors and windows closed 20 min prior to the experiment. After 60 min of the fragrance exposure, HR and BP were measured. Administration of ylang ylang EO resulted in significant reduction of both HR and BP, with a concomitant relief of the arousal level in the autonomic nervous system (Jung et al., 2013). Consistent with these results, in another human study consisting of 10 healthy volunteers, numerous physiological parameters were evaluated before and after ylang ylang EO inhalation. Both, systolic and diastolic BP were significantly reduced as well as the pulse rate 3 min after inhalation. Alpha brain waves, which are present in deep relaxation, were found to increase, suggesting that a decrease in stress level was produced. This result was supported further with a decrease in stress index values from high to medium levels, which was determined by measuring variations in salivary alpha-amylase (Pujiarti et al., 2012). Moreover, Ishiguchi, Saitou, Suenaga, Ohta, and Matsuura (2008) also reported that ylang ylang EO inhalation significantly increased alpha brain waves in a study consisting of 20 healthy volunteers. This effect was concomitant with a reduced amplitude of auditory P300, which is associated with higher cognitive processing (Table 2). Additionally, volunteers were subjected to VAS after inhalation, which resulted in a decreased level of alertness. Similarly, Watanabe et al. (2013) showed that inhalation of ylang ylang EO reduced the P300 amplitude in healthy subjects, reducing information processing resources when an auditory oddball task was performed. More recently, in a rodent study, the aroma exposure has been shown to reverse anxiety in mice through the extracellular signal-regulated kinase 1/2/CREB pathway (in the hippocampus) and affect the serotonergic system (Zhang et al., 2018). Inhalation of ylang ylang EO (0.1%, 1%, and 10%, v/v) in anxious mice increased both the number of entries and the time in the open arms in the elevated plus maze (EPM). Western blot analysis showed that exposure to the oil down-regulated both CREB and c-Fos in the hippocampus. Both a reduced blood plasma corticosterone level and an altered brain serotonin metabolism were observed after ylang ylang EO administration (Zhang et al., 2018). In a previous study, Zhang et al. (2016) found that acute and chronic ylang ylang EO inhalation produced a higher anxiolytic effect in male mice compared to female mice. Both treatments increased the time that mice visited light box area and open arms in the light–dark box (LDB) and EPM tests, respectively. In the male mice, an increased concentration of 5-HT in the hippocampus was observed while the dopamine concentration decreased in the striatum. Benzyl benzoate was found to be the main active compound in ylang ylang EO exerting the anxiolytic effects through the 5-HTergic and DAergic pathways (Zhang et al., 2016). Taken together, the findings described above indicate that the HPA axis, and the serotonergic and DAergic pathways are implicated in the anxiolytic and antidepressant effects of ylang ylang EO (Table 1).
FIGURE 3 The effects of essential oils on the nervous system. (a–e) Schematic representation of stress-response modulating systems. (a) hypothalamic–pituitary–adrenal (HPA) axis and (c) efferent vagus nerve (blue pathways) conform the anti-inflammatory response to stress whereas (b) the sympathetic nervous system displays an inflammatory response (red pathways). Stressors stimulate the release of the CRH in the paraventricular nucleus (PVN), promoting the synthesis and secretion of the adrenocorticotropic hormone (ACTH) by the pituitary gland. ACTH then induces the synthesis and release of glucocorticoids (cortisol in humans and corticosterone in rodents) in the adrenal glands. Glucocorticoids and acetylcholine (ACh) bind to receptors on cytokine producing cells producing an anti-inflammatory response. (F) Under persistent HPA activation, corticosteroids can decrease serotonin (5HT) and dopamine (DA) levels in the brain leading to anxiety disorders or depression. (g) Frankincense, ylang ylang, bergamot, neroli, sweet orange, geranium and rose essential oils (EOs) can affect hypothalamic–pituitary–adrenal axis by decreasing glucocorticoid levels producing a calming effect and showing a decrease in blood pressure (BP) and heart rate (HR). (b) Stressors stimulate the sympathetic nervous system by releasing noradrenaline (NA) and adrenaline (AD) from sympathetic nerves and the adrenal gland respectively. NA and AD, then bind to the cytokine producing cells activating the transcription of the nuclear factor kappa-light-chain-enhancer (NF-kB), which in turn, promotes the transcription and release of proinflammatory cytokines (IL-1, IL-6 and TNF-α). These cytokines can then cause cognitive, emotional and behavioral alteration by either stimulating the afferent vagus nerve or by crossing the blood–brain-barrier and interacting with various neurotransmitter systems such as serotonergic and DAergic circuits. (h) Cinnamon EO exerts its anxiolytic effect by suppressing the transcription of NF-kB. (i) Ylang-ylang and rose EOs produce an anxiolytic effect by increasing serotonin levels in the brain and decreasing glucocorticoid serum concentration. (j) Lemongrass and bergamot EOs promote an anxiolytic effect by GABAergic system activation. (k) Rosemary, clary sage and roman chamomile EOs activate the DAergic system producing beneficial cognitive effects. Clary sage EO acts as a memory enhancer whereas roman chamomile EO displays psychostimulant effects. Rosemary EO exhibits both a psychostimulant effect and it enhances memory [Colour figure can be viewed at wileyonlinelibrary.com]
4.3 | *Cinnamomum verum* (cinnamon) EO

Cinnamon EO is extracted from the brown bark of *Cinnamomum verum*, also known as true cinnamon tree or Ceylon cinnamon tree. Native to Southern India and Sri Lanka (Sohrabi, Pazgoohan, Seresht, & Amin, 2017), 15 compounds have been identified in cinnamon EO. The majority of these are phenolic compounds followed by sesquiterpene hydrocarbons and a minority of monoterpenic hydrocarbons. The main component is trans-cinnamaldehyde, which has been reported to represent 65%–85% of cinnamon bark and is considered to be the main active compound (Sohrabi et al., 2017). In a rodent study, intraperitoneal (i.p) injection of cinnamon EO was shown to produce antidepressant-like effects in albino male mice. Doses of 0.5, 1, and 2 mg/kg of the EO were injected intraperitoneally in both acute (3 injections in 24 hr) and subacute drug administration (one injection per day for 14 days). Subacute administration decreased the immobility time in both, forced swim test (FST) and tail suspension test (TST) in a dose-dependent manner. The 2 mg/kg mice group not only spent longer time into the open arms of EPM but also had more entries when compared with controls (Sohrabi et al., 2017). Although the molecular mechanism underlying the antidepressant-like effects was not elucidated in this study, the authors suggested that a suppression of neuroinflammation could be involved. This mechanism could have been the result of the down-regulation of inducible nitric oxide synthase, cyclooxygenase-2, TNF-α; and suppression of NF-kB and p53 in activated B cells pathways (Chen et al., 2016). Although there is a lack of direct evidence for the molecular mechanisms involved in the antidepressant-like effects of cinnamon EO, another mechanism has been suggested. Animal experiments have shown that intravenous (i.v) administration of TCA increase adrenaline secretion via adrenal sympathetic nerves and activation of the sensory nerves expressing thermosensitive transient receptor potential channels A1 (Iwasaki, Tanabe, Kobata, & Watanabe, 2008). This could be beneficial for treatment of decreased monoamine-related depressive disorders, in which the levels of adrenaline are decreased. Altogether, these studies (Table 1) indicate that the mechanism of action of cinnamon EO remains elusive and warrants more investigation.

4.4 | *Citrus aurantium* (Neroli) EO

Neroli EO is extracted by steam distillation from the flower of the bitter orange tree (*Citrus aurantium*). The most abundant components of this oil are limonene, β-myrcene, and β-pinene (Costa et al., 2013). In an animal experiment, inhalation of neroli EO significantly increased the swimming time of gerbils (65%) during the FST, showing an attenuation of the levels of anxiety. However, when the locomotor activity was studied through a multi-box ActiMot detection system, inhalation of neroli EO did not seem to exert any effect (Chen et al., 2008). Inhalation of neroli EO (0.1% or 0.5%; 5 min, twice per day for 5 days) was shown to significantly decrease levels of stress and alleviate undesirable menopausal symptoms in a double-blind, randomized controlled trial performed to 36 healthy postmenopausal women (Choi et al., 2014). Reduced levels of stress, and improved physical conditions were detected by the subjective methods Stress VAS and the Menopause-Specific Quality of Life Questionnaire (MENQOL), respectively. Significant reductions in both systolic and diastolic BP were also observed after inhalation of the oil (Choi et al., 2014). Also, in a randomized clinical study, Namazi et al. (2014) studied the anxiolytic effects of neroli EO during the first stage of labor. A total of 126 subjects comprised the study, consisting of two groups of 63 subjects each: for intervention (neroli EO) and control (saline solution) treatments. For both groups, the compounds were provided to subjects using gauzes impregnated with 4 mL of each solution, attached to a collar, which were replaced every 30 min until delivery. Anxiety was assessed at baseline and at dilutions of 3–4 and 6–8 cm using Spielberger State–Trait Anxiety Inventory (STAI), which was found significantly lower in the group treated with the EO (Namazi et al., 2014). Summarizing, these results (Table 1) suggest that the anxiolytic effects of neroli EO could be the result of an interaction with the HPA axis. However, further animal studies are needed to decipher the involvement of neurotransmitter systems in the calming effect of neroli EO.

4.5 | *Citrus bergamia* (bergamot) EO

Bergamot EO is obtained from the epicarp and mesocarp of *Citrus bergamia*, Risso fruit. The major compounds in this EO are limonene, lineryl acetate, and linalool (Rombolá et al., 2017). Bergamot EO is known for its ability of minimizing symptoms of both stress-induced anxiety and mild mood disorders. In a rodent study, significant increments in the extracellular concentrations of amino acid neurotransmitters in rat hippocampus were found after the administration of bergamot EO. Administration of the oil (100 μL/kg, i.p) significantly increased the extracellular release of the amino acids aspartate, glycine and taurine in a Ca²⁺-dependent manner. On the other hand, the release of aspartate, glycine, taurine, glutamate, and GABA was found to increase independently of Ca²⁺ when the oil was perfused into rat hippocampus via dialysis probe (20 μL/20 min). This study suggested that bergamot EO may interfere with the exocytotic machinery involved in neurotransmitter release. Hence, the receptor-mediated mechanisms that regulate the synaptic levels of amino acid neurotransmitters might be involved in the mode of action of bergamot EO (Morrone et al., 2007). Moreover, Rombolá et al. (2009) studied the systemic effects of bergamot EO in both gross behavior and electrical activity in the brain of rats. Gross behavioral changes in immobility, locomotor activity, stereotyped movements (grooming, licking, rearing, and sniffing), and squatting posture were all recorded during the experimental period. Encephalograms were obtained from the hippocampus and cerebral cortex for further analysis by Fast Fourier Transformation to determine the energy in the single frequency bands of the spectra. Increments in systemic administration (i.p injection) of the oil were shown to produce dose-dependent increase in both, the locomotor and exploratory activity in rats, accompanied with a significant
increase in the energy of the faster frequency bands in the electroencephalogram (EEG) spectrum (Rombolà et al., 2009). In another rodent study using male rats, the anxiolytic effect of the inhalation of bergamot EO (1.0%, 2.5%, and 5.0% w/w) was evaluated and compared with that of diazepam (DZP) injection (1 mg/kg, i.p.) by EPM and hole board tests (HBT). Stress-induced corticosterone was also measured from plasma samples before and after treatment. Both treatments, inhalation of bergamot EO (1.0% and 2.5%) and injection of DZP showed a significant increase in both the percentage of open arm entries and time in the open arms in the EPM test. Furthermore, in the HBT, bergamot EO (2.5% w/w) and DZP significantly increased the number of head dips. Additionally, an attenuated corticosterone response to acute stress was observed when the EO (2.5% w/w) and DZP were administrated showing a diminished HPA axis activity (Saiyudthong & Marsden, 2011).

In another animal experiment, Rombolà et al. (2017) investigated the anxiolytic, sedative and antidepressant effects of bergamot EO and DZP in rats by the behavioral tests; open field test (OFT), EPM, and FST. In the OFT, only bergamot EO (500 μL/kg) produced a significant decrease in anxiety-related behaviors including crossing, rearing, and wallrearing compared to the vehicle group (jojoba oil). Both the EO (250 and 500 μL/kg) and DZP (1.2 mg/kg) significantly decreased grooming showing their anxiolytic effects. However, only bergamot EO produced a significant increment in immobility suggesting a sedative effect. In the EPM, only DZP (5 mg/kg) significantly increased both, the number of entries and time in the open arms. Conversely, in the FST, only bergamot EO (250 and 500 μL/kg) significantly increased the immobility time suggesting that this oil supported an adaptation behavior in response to a hostile environment. Although this study showed the anxiolytic/relaxant-like effects of bergamot EO through behavioral tests, the results were not superimposable to those of the DZP (Rombolà et al., 2017). In a random crossover study consisting of 41 healthy women, inhalation of bergamot EO diluted in water was shown to produce both, psychological and physiological effects. After 15 min of inhalation of the oil, followed by 10 min rest, significantly decreased values of salivary cortisol. High-frequency, which is an indicator of the parasympathetic nervous system activity, was found to increase during the 10 min of rest after inhalation. Profile of Mood State (POMS) and STAI tests, used to accesses emotions and fatigue after inhalation of the EO, showed that the mood of the volunteers improved considerably (Watanabe et al., 2015). In another human study, Han et al. (2017) studied the effects of inhalation of bergamot EO on mental health and well-being by using the Positive and Negative Affect Scale (PANAS) in 57 volunteers aged 23–70 years. Patients were told that the aim of the study was to evaluate the effect of the waiting time on their feelings to avoid any distraction related with the EO scent, which was produced by a diffuser in the waiting room. In accordance with previous studies, a significant increase (17% higher) of positive feelings was observed in the participants after exposure to bergamot EO for 15 min (Han et al., 2017). Taken together, these findings (Table 1) show that both the HPA axis and the GABAergic system are involved in the anxiolytic and antidepressant properties of bergamot EO.

4.6  Citrus sinensis (sweet orange) EO

Sweet orange EO is obtained from the peel of the evergreen tree Citrus sinensis L using cold pressing. The main volatile compounds are d-limonene, β-myrcene, α-pinene, sabine, linalool, geranial, and neral (Dosoky & Setzer, 2018). This EO has shown strong anxiolytic activities in both, human and animal studies. In a human study, the anxiolytic activity after 90s inhalation of sweet orange and rose EOs was assessed in 20 female university students (mean age 22.5 ± 1.6 years) using near-infrared time-resolved spectroscopy and a modified semantic differential approach to study the physiological and subjective effects of the oils, respectively. After intervention, both EOs were found to display a significant decrease in oxyhemoglobin concentration in the right prefrontal cortex as well as an increase in the reported feelings “comfortable” and “relaxed” as perceived by the volunteers (Igarashi, Ikei, Song, & Miyazaki, 2014). In another human trial, Lehrner, Marwinski, Lehr, Johren, and Deecke (2005) assessed the anxiolytic effects of both sweet orange EO and lavender EO in dental patients. Two hundred patients aged 18–77 years (half women, half men) were evenly distributed in four independent groups; sweet orange EO, lavender EO, music, and control conditions. An electrical dispenser was used to administrate the EOs and was placed in the waiting room hidden from each individual. Anxiety level was accessed by STAI and Mehrdimensionale Befindlichkeitsfragebogen (MDBF) to evaluate current mood, alertness, and calmness. Consisting with previous studies, they found that patients who were exposed to the EOs had significantly lower level of anxiety, a more positive mood, and a higher level of calmness compared to the control group (Lehrner et al., 2005). Furthermore, in a randomized controlled clinical trial, Jaafarzadeh et al. (2013) demonstrated the anxiolytic effects of sweet orange EO in 30 children before and after dental treatment. The patients consisted of 10 boys and 20 girls, aged 6–9 years, which were separated in two groups, intervention and control groups. Anxiolytic effects were assessed by measuring salivary cortisol and HR, which were found significantly lower compared to control (Jaafarzadeh et al., 2013) after treatment. Moreover, in another human study, sweet orange EO has also been shown to have anxiolytic properties in healthy volunteers. Forty men were allocated in three different groups; test aroma (sweet orange EO), aroma control (tea tree EO), and nonaromatic control (water). After inhalation, all the groups were subjected to the video-monitored version of the model of anxiety Stroop Color-Word Test (SCWT). Psychologic parameters including state-anxiety, subjective tension, tranquilization, and sedation, were assessed by STAI and Visual Analogue Mood Scale (VAMS) while physiological parameters were evaluated by measuring HR and electromyography of the gastrocnemius muscle. The two control groups showed a significant increase in state-anxiety and tension and a significant decrease in tranquility after SCWT whereas the psychological parameters were not affected in the group that inhaled sweet orange EO. Although the physiological parameters were not altered in any of the groups, the tranquilizing effects of sweet orange EO were demonstrated by STAI and VAMS tests (Goes, Antunes, Alves, & Teixeira-Silva, 2012). The anxiolytic activities of sweet orange EO.
have also been demonstrated in male rats by both the EPM and the LDB. After inhalation of the EO (100, 200, or 400 μL) for 5 min, a significant increase in the exploration activity was observed in both, the open arms (time: p = .004; entries: p = .044) and in the lit chamber (time: p = .030) when the highest concentration (400 μL) was used showing an acute anxiolytic activity (Faturi, Leite, Alves, Canton, & Teixeira-Silva, 2010). Summarizing, the strong anxiolytic properties of sweet orange EO seem to be the result of an interaction of the oil with HPA axis (Table 1). However, further animal studies need to be performed to study the involvement of neurotransmitter systems in its calming effects.

### 4.7 | Cymbopogon citratus (lemongrass) EO

Lemongrass EO is extracted from the leaves of *Cymbopogon citratus* primarily by hydrodistillation (Costa et al., 2011). The major compound of this EO is citral, which is a mixture of neral and geraniol constituting approximately 70%–85% of the oil, followed by β-myrcene (Blanco, Costa, Freire, Santos, & Costa, 2009). Other compounds that can be found in this oil include limonene, citronellol, geraniol, 1,8-cineole, nerol, α-terpineol, borneol, eugenol, geranyl acetate, and elemicin (Ekpenyong & Akpan, 2017). Lemongrass EO has shown anxiolytic activity in the LDB test in male rats at a dose of 10 mg/kg (p.o.). In order to investigate the mode of action of this EO, flumazenil, a competitive antagonist of BDZ binding was injected (i.p.). Flumazenil showed to reverse the effect of lemongrass EO in the LDB suggesting that its mode of action can occur via the GABAA receptor–BDZ complex (Costa et al., 2011). Consistent with these results, anxiolytic activity of lemongrass EO was demonstrated by both EPM and LDB procedures in Swiss male mice. A dose of 1.0 g/kg orally administered (p.o) was found to increase the percentage of both entries and time spent in the open arms and in the lit chamber in EPM and LDB respectively. Additionally, the same dose (1.0 g/kg) was shown to have sedative activity through pentobarbital sleeping time test. After administration of the oil (p.o), significant increase in the sleeping time was observed compared to control (Blanco et al., 2009). Moreover, in order to evaluate the anxiolytic properties of lemongrass EO in humans, 40 men (aged 18–30) were subjected to the video-monitored version of SCWT to produce an anxious state. After exposure to the aroma (three and six drops), a significant reduction of anxiety and subjective tension was shown compared to control group, which was assessed by both STAI and Social Phobia Inventory (SPIN) questionnaire (Goes, Ursulino, Almeida-Souza, Alves, & Teixeira-Silva, 2015). Taken together, these experiments (Table 1) indicate that the anxiolytic effect of lemongrass EO can be the result of an interaction of its components with the GABAergic neurotransmitter system.

### 4.8 | Lavandula angustifolia (lavender) EO

Lavender EO is extracted by steam distillation from the flowers of the evergreen shrub *Lavandula angustifolia* Mill (Demasi et al., 2018). The major compounds of lavender EO are linalyl acetate, linalool, lavandulyl acetate, myrcene, terpen-4-ol, -terpineol, cis-linalool oxide, trans-linalool oxide and ocimene. Inhalation of lavender EO is a popular anxiolytic alternative therapy to treat mild stress and anxiety in Europe and the United States (Bradley, Starkey, Brown, & Lea, 2007a). Pioneer studies have previously shown the involvement of the GABAergic system in the anxiolytic and antidepressant properties of lavender essential oil (Aoshima & Hamamoto, 1999; Guillmain et al., 1989). In an in vivo study, lavender EO inhalation was shown to decrease stress levels in both, male and female gerbils. The animals were subjected to inhalation of the EO daily over a period of 2 weeks for 30 min resulting in a significant increase in the open entries in the EPM assessment. These results were similar to the effect obtained using D2P (1 mg/kg i.p.) in the same study (Bradley et al., 2007a). Furthermore, lavender EO has also shown its effectiveness in alleviating the symptoms of premenstrual syndrome (PMS). In a randomized controlled trial, five sessions of aromatherapy were applied to an intervention group of 40 students during three menstrual cycles. The effects were investigated through the PMS scale questionnaire, which assesses varying symptoms of PMS including anxiety, depressive affect, nervousness, pain, bloating and depressive thoughts. These symptoms were found to have been significantly reduced in the intervention group after treatment compared to the control group (37 students) (Uzunçakmak & Ayaz Alkaya, 2018). Similarly, in another human study consisting of 30 healthy volunteers, inhalation of lavender EO was shown to have anxiolytic and analgesic properties through a stress assessment questionnaire and bispectral index (BIS), respectively. After 5 min of the treatment with a face mask, the stress values and BIS values were significantly decreased in the intervention group (Kim et al., 2011). In a clustered randomized-controlled trial, anxiety of 340 patients divided in two groups (under lavender EO odor vs. with no odor) was assessed while waiting for and scheduled dental appointment. Although both groups showed the same levels of generalized anxiety as assessed by the Modified Dental Anxiety Scale (MDAS), current anxiety evaluated by STAI-6 was found to be significantly lower in the intervention group (Kritsidima, Newton, & Asimakopoulou, 2010). Moreover, inhalation of lavender EO has also been shown to restrain the decrease of attention during a vigilance task. In a human study performed in 15 healthy patients, Shimizu et al. (2008) showed that the reaction time was significantly reduced when the participants inhaled the EO compared to control (mixed gas with no odor). These results demonstrated the effectiveness of lavender EO in helping to maintain sustained attention during long-term tasks (Shimizu et al., 2008). Interestingly, lavender EO has also shown therapeutic effects in psychotic patients. In a randomized, double-blind, placebo-controlled trial, 221 adults suffering from clinically diagnosed anxiety disorder were treated with silexan (80 mg/day), which is an oral lavender oil, or placebo for 10 weeks. Every 2 weeks, patients were requested to take the Hamilton Anxiety Scale (HAMA) and the Pittsburgh Sleep Quality Index (PSQI) assessments (primary outcome measures) whose scores were shown to decrease until week 10. Additionally, the Clinical Global Impressions scale, the SF-36 Health Survey Questionnaire, and the Zung Self-rating Anxiety Scale...
were used as secondary efficacy measures. The treatment with silexan showed a significant beneficial effect on the quality and duration of sleep while improving general mental and physical health without presenting unwanted side effects. Moreover, this lavender oil preparation has been demonstrated as safe for the relief of anxiety disorder symptoms (Kasper et al., 2010). In summary, lavender EO has been proven to be a reliable anxiolytic alternative for healthy and psychotic patients, whose effects are related to an interaction with the GABAergic system (Table 1, 2).

4.9 | **Citrus paradisi** (grapefruit) EO

Grapefruit EO is obtained from the fruit mesocarp of *Citrus paradisi*, mostly by cold-pressing. The major compound of this EO is limonene followed by R-terpinene, R-pinene and sabine. Additionally, traces of R-Thujene, R-pinene, γ-terpinene, and terpinolene can also be found in grapefruit EO (González-Mas, Rambla, López-Gresa, Amparo Blázquez, & Granell, 2019). In a randomized controlled study, the anxiolytic activity of grapefruit EO was assessed in 361 patients undergoing colonoscopy using the Numeric Rating Scale (NRS). Abdominal discomfort was found significantly attenuated after inhalation of the oil in patients with high anxiety, showing its effectiveness as a supplementary treatment for anxious patients undergoing colonoscopy (Table 1) (Hozumi et al., 2017). However, the molecular mechanisms involved in the anxiolytic action of grapefruit EO remain unknown. Therefore, further animal and human studies are needed.

4.10 | **Pelargonium graveolens** (geranium) EO

Geranium EO is obtained mainly by distillation of the aerial part of *Pelargonium graveolens* (Ali et al., 2015). This EO is comprised of more than 32 chemical compounds, where the majority are monoterpenes (68.98%). The main compounds are b-citronellol, citronellyl formate, geraniol, 10-epi-g-eudesmol, geranyl formate and (I)-linalool (Boukhris, Simmonds, Sayadi, & Bouaziz, 2013). The anxiolytic effect of geranium EO was evaluated in a randomized, triple-blind, placebo-controlled clinical trial in 80 patients with acute myocardial infarction. The levels of anxiety during the experiment were assessed using STAI. Absorbing patches containing three drops of either geranium EO or placebo (sunflower oil) were attached inside the oxygen masks of the intervention and control groups respectively. Both groups were asked to inhale the oils for 20 min for 2 days, resulting in a significant reduction of anxiety in the intervention group (Shirzadegan, Gholami, Hasanvand, Birjandi, & Beiranvand, 2017). Similarly, in another clinical study, the anxiolytic effect of geranium EO was evaluated in 100 nulliparous women using a fabric attached to the participant’s collar. The levels of anxiety were assessed using STAI before and 20 min after medical intervention. Both anxiety scores and the diastolic BP were significantly reduced after inhalation of the EO compared to control (Rashidi Fakari et al., 2015). These results (Table 1) suggest that geranium EO may exert its anxiolytic effects by interacting with the HPA axis. Nevertheless, further studies are needed to decipher the contribution of neurotransmitter system in the calming effect of geranium EO.

4.11 | **Rosa damascena** (rose) EO

Rose EO is obtained by hydrodistillation from the flowers of *Rosa damascena* generally. The chemical composition of this EO consist of more than 45 molecules, from which the majority are monoterpenic alcohols. The major compounds of rose EO are 2-phenethyl alcohol, citronellol, geraniol, methyl eugenol and eugenol (Umezu, Ito, Nagano, & Yamakoshi, 2002). The sedative effects of rose EO were evaluated in a randomized controlled trial, consisting of 60 patients hospitalized in a coronary care unit. Each night, a paper towel attached to each patient’s pillow was impregnated with two drops of the EO and left for 8 hr. The treatment was performed for three consecutive days and the sleep quality was assessed by the PSQI, which resulted in significantly better quality of sleep in the intervention group compared to the control group which received routine care (Hajibagheri, Babai, & Adib-Hajbaghery, 2014). In another human study consisting of 40 healthy volunteers, the anxiolytic effect of the transdermal absorption of rose EO was assessed by measuring autonomic parameters and rating scales. The treatment with the EO was shown to decrease RR, blood oxygen saturation and systolic BP showing a decrease in the autonomic arousal. Moreover, the intervention group was more relaxed and less alert compared to the control group (Hongratana, 2009). In a rodent study, De Almeida, Motta, De Brito Faturi, Catalani, and Leite (2004) investigated the effect of rose EO inhalation (1.0%, 2.5%, and 5.0% w/w) in adult male rats using the EPM test and compared with DZP (1.0 and 2.0 mg/kg, i.p.). Inhalation of the oil resulted in a significant increase in both the number of visits and time spent in the open arms of the EPM. These anxiolytic properties were comparable with DZP (De Almeida et al., 2004). In another animal model, mature gerbils were exposed to acute (24 hr), and chronic (2 week) olfactory administration of rose EO and the anxiolytic effect was accessed using the EPM and LDB. In the EPM, increase in exploration was observed in the intervention group whereas in the LDB, both anxiolytic spatiotemporal and exploratory behavior effects were increased. The anxiolytic effects were increased after chronic exposure to rose EO. The authors suggested that the anxiolytic profile produced by rose EO was similar to that characteristic of serotonergic drugs rather than BDZ type drugs (Bradley, Starkey, Brown, & Lea, 2007b). Taken together (Table 1), HPA axis and the serotonergic system seem to be involved in the anxiolytic effects of rose EO.

4.12 | **Rosmarinus officinalis** (rosemary) EO

Rosemary EO is extracted from the aerial parts of *Rosmarinus officinalis*, mainly by hydrodistillation. The chemical composition of this EO consist of more than 16 chemical compounds, in which the major components are cineole, camphor, α-pinene, camphene and α-terpineol (Elyemni et al., 2019). Rosemary EO has been reported to improve cognition, memory, and mood; and has also shown
remarkable anxiolytic properties (Table 1, 2) (Villarel et al., 2017). In an animal model, mice were allowed to inhale rosemary EO to evaluate its anxiolytic effect. After inhalation of the oil, a significant decrease in the immobility time in the TST and in serum corticosterone level was observed along with a concomitant increase of brain dopamine (DA) levels (Villarel et al., 2017). Rosemary EO was found to activate the stress response system through the HPA axis and the nerve growth factor pathway. The authors suggested that these effects could be attributed to the active compound α-pinene, which is known for its anxiolytic properties. In a clinical trial consisting of 20 healthy patients, rosemary EO showed its stimulatory properties through the measuring of a range of autonomic nervous system parameters. Inhalation of the oil produced significant increments in BP, HR, and RR. Mood state was evaluated by Geneva Emotion and Odor Scale (GEOS), which resulted in a more active after treatment as reported by the intervention group. EEG analysis was also performed showing a decrease in the power of alpha1 (8–10.99 Hz) and alpha 2 (11–12.99 Hz) waves while the beta wave (13–30 Hz) power was increased in the anterior region of the brain (Sayorwan et al., 2013). In a human trial the olfactory impact of rosemary EO and lavender EO on the CNS, cognitive functions (e.g., memory, attention, etc.) and mood were assessed using CDR computerized cognitive assessment and VAS mood questionnaires, respectively. The study consisted of 140 healthy participants that were randomly assigned to three independent groups, rosemary EO, lavender EO, and no odor. The resulting outcomes of the performance revealed that rosemary EO significantly enhanced the overall quality of memory and secondary memory factors compared to the control group, while lavender EO significantly decreased the performance of working memory and impaired reaction times in attention and memory-based tasks. Both the control and lavender EO groups were found to be significantly less alert compared to the rosemary EO group after the experiment. However, the two intervention groups were registered to be more content compared to the control group after the intervention (Moss et al., 2003). Altogether, these findings (Table 2) indicate that rosemary EO can improve memory through activation of the DAergic system.

4.13 | *Salvia sclarea* (Clary sage) EO

Clary sage EO is obtained mainly by hydrodistillation of the aerial part of *Salvia sclarea*. The main components of this EO include linalool, α-terpineol, geraniol, acetate derivative of geraniol, and myrcene (Table 1) (Kuzma et al., 2009). In an animal study, clary sage EO was administrated to Sprague–Dawley rats by either intraperitoneal injection or inhalation. Pre-treatment with buspirone (5-HT1A agonist), SCH-23390 (DA1 receptor antagonist) and haloperidol (DA2, DA3, and DA4 receptor antagonist) significantly blocked the antidepressant effect of the EO in the FST (decreased immobilization). These results show that modulation of the DAnergic pathway is involved in the antidepressant effect of clary sage EO (Seol et al., 2010). A double-blind randomized controlled trial for clary sage EO was performed in 34 female patients with urinary incontinence. Patients were requested to inhale the oil for 60 min during urodynamic examination. After treatment with the EO, a significant decrease in systolic and diastolic BP as well as a concomitant decrease in the RR were reported showing its remarkable anxiolytic properties (Seol et al., 2013).

4.14 | *Anthemis nobilis* (Roman chamomile) EO

Roman chamomile EO is extracted often by steam distillation from the flower heads of *Anthemis nobilis* (syn. *Chamaemelum nobile* (L.). Although diverse extracts of roman chamomile are well-known for their anxiolytic and sedative activities, a recent study has shown that the EO produced by steam distillation has psychostimulant effects. Umezu et al., 2017 identified and studied the effects of Roman chamomile EO constituents on the CNS in male mice by using the tilting type ambulometer test (Table 2). Isobutyl angelate, isoamyl anglate and 2-methylbutyl isobutyrate were identified as the major active constituents responsible for the ambulatory-promoting effects of roman chamomile, which accounted for about 75% of the EO. Minor compounds such as 2-methylbutyl angelate, pinocarveol and pinocarvone were also detected. Isobutyl angelate, isoamyl anglate, 2-methylbutyl isobutyrate and 2-methylbutyl angelate have been previously detected in Roman chamomile EO (Omidbaigi et al., 2003; Rossi, Melegari, Bianchi, Albasini, & Vampa, 1988). Umezu et al., 2017 compared the effects produced by Roman chamomile EO with a mix of isobutyl angelate, isoamyl anglate and 2-methylbutyl isobutyrate in male mice. The mixture did not fully replicate the effect of the EO suggesting that the minor components also made a contribution toward the total effect. They also examined the role of DA in the ambulation-promoting effects produced by the mixture of active compounds using the DA antagonists chlorpromazine and haloperidol (HAL). Chlorpromazine and HAL produced a significant reduction in the ambulation-promoting effects suggesting that the DA neurotransmitter system may be involved in the psychostimulant effect. The lack of the flavonoid, 7,4’-dihydroxyflavone (apigenin) in this Roman chamomile EO could explain the absence of a specific calming effect. Furthermore, apigenin is known to significantly contribute to the sedative and anxiolytic effects of Roman chamomile aqueous extracts by binding to GABA<sub>A</sub> receptors (Viola et al., 1995; Umezu et al., 2017). Furthermore, Umezu (2012) had previously showed the stimulant-like effects of Roman chamomile EO and peppermint EO in the CNS by using a discrete shuttle-type conditioned avoidance task in male mice. After administration of Roman chamomile EO (200–3,200 mg/kg, i.p) and peppermint EO (50–800 mg/kg, i.p) a significant increase of the avoidance response rate (number of shutttings/min) was observed (Umezu, 2012).

4.15 | *Pogostemon cablin* (patchouli) EO

Patchouli EO is extracted predominately by hydrodistillation from the leaves of *Pogostemon cablin*. Nineteen compounds have been identified in this EO, the major components being patchoulool, δ-guaiene, α-guaiene, α-Gurjune, seychellene, viridiflorol, β-caryophyllene and
β-patchoulene (Kusuma & Mahfud, 2017). Pujjarti et al. (2012) demonstrated the stimulatory effect of patchouli EO in human physiology. Systolic and diastolic BP was observed to increase 3 min after sniffing the oil while the alpha wave also increased (Pujjarti et al., 2012). Although the stimulant properties of patchouli EO have been demonstrated by measuring physiological parameters (Table 2), further studies are needed to evaluate the contribution of neurotransmitter system to the psychological effect in humans.

4.16 | Mentha piperita (peppermint) EO

Peppermint EO is often obtained by stem distillation from the leaves of Mentha piperita. The chemical composition of this EO consist of more than 26 compounds, in which the majority are oxygenated monoterpene being menthol and isomenthone the main components (Hsouna et al., 2019). Moss et al. (2008) assessed the effects of peppermint EO on cognitive performance in 144 volunteers by using a CDR computerized assessment battery. Peppermint was found to enhance memory while increasing alertness compared to control (Table 2) (Moss et al., 2008). However, more studies are needed to elucidate the molecular pathways involved in the memory-enhancing properties of this peppermint EO.

4.17 | Salvia officinalis (sage) EO

Sage EO is extracted mainly by hydrodistillation from the leaves of Salvia officinalis. The chemical composition consists of approximately 49 compounds in which camphor, α-thujone, 1,8-cineole, viridiflorol, β-thujone and β-caryophyllene are the main components (Ben Khedher, Ben Khedher, Chaieb, Tounsi, & Hammami, 2017). Sage EO has been shown to improve memory performance in a human trial of 45 healthy volunteers accessed by Prospective Remembering Video Procedure (PRVP). The intervention group showed significantly improved performance during the task compared to control groups (Moss, Rouse, & Moss, 2014). Additionally, in a previous study by Moss, Rouse, Wesnes, and Moss (2010), the cognitive performance was assessed via CDR system in 135 healthy patients. Moreover, Bond–Lader mood scales were used to measure the participants' mood before and after the cognitive tasks. The quality of memory and secondary memory were found to improve significantly in the group subjected to sage EO aroma (Table 2) (Moss et al., 2010). Nevertheless, further studies are required to decipher the molecular mechanisms involved in the memory-enhancing effects of sage EO.

5 | CONCLUSIONS

The increasing experimental research in the pharmacology of EOs during the last 15 years has revealed a diverse range of neural pathways in their mode of action allowing a more comprehensive understanding of their physiological and psychological effects. EOs have proved their neuropharmacological effects in animal models by showing a significant influence in the HPA axis, the sympathetic nervous system and in neurotransmitter systems including serotonergic, DAergic and GABAergic systems. This interaction with a variety of CNS receptors results in measurable physiological changes that can produce measurable psychological effects. Clinical trials have showed evidence for a range of physiological and psychological responses to the inhalation of EOs such as changes in HP, BP, RR, cortisol serum levels and brain wave composition accompanied with relaxation, contentment, and alertness feelings. The ability of EOs to trigger different neural pathways without having the side effects of synthetic drugs makes them potential alternatives for treatment of mental illnesses including depression, anxiety, and dementia. However, due to their synergetic effects and complex receptor-EO compound interaction, greater research must be done, especially in clinical research to promote the development and acceptance of EO-based drugs.

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CONFLICT OF INTEREST

I wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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