



Review of Essential Oil Bioactivity Against Anxiety Symptom

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Abstract: The use of essential oils as complementary therapy for various health conditions, especially those involving the central nervous system (CNS), is gaining increased attention. Anxiety disorder, a common CNS-related condition characterized by excessive worry and fear, is one of the main targets for such therapies. Essential oils from various plants contain bioactive compounds that act on the CNS and exhibit anxiolytic potential. This systematic literature review aimed to assess the anxiolytic bioactivity of essential oils and identify the most effective types used for anxiety reduction. Preclinical studies from seven journals revealed that essential oils such as Agarwood, Bergamot, Cananga odorata, Ocimum basilicum, Lavender, Nectandra grandiflora, and Cinnamon influence animal behavior linked to anxiety reduction. Clinical reviews from eleven studies found that Lavender oil, especially due to its linalool content, was the most commonly used essential oil for lowering anxiety levels. The mechanisms include inhibition of CRF, ERK1, and CREB, antagonism of NMDA receptors, inhibition of SERT, and modulation of GABA_A receptors and calcium influx. In conclusion, essential oils exhibit various bioactivities affecting the CNS, supporting their role as potential anxiolytic agents.

Keywords: Anxiety; Anxiolytic; Bioactivity; Essential oil

Introduction

Herbal plants have been widely used for the treatment of diseases around the world. Evaluation of the effects of this plant on organs and systems of the body has contributed to the development of a scientific basis for therapy and has been used for the treatment of several diseases (Sharmeen et al., 2021). Essential oils are obtained from the extraction of plants that have a unique aroma and complex chemical components (Özkaraman et al., 2018). Extraction of aromatic plant materials such as leaves, rhizomes, flowers, roots, bark, seeds, fruits, woods and whole parts of the plant can produce essential oils. The biological activity of essential oils depends on the part of the plant being extracted. Antioxidants, antimicrobials, antivirals, anti-mutagenic, anticancer, anti-anxiety and many other biological activities have been tested against essential oils (Morsy, 2017). Monoterpenes and sesquiterpenes,

carbohydrates, phenols, alcohols, ethers, aldehydes, and ketones are important compounds in essential oils (Yammine et al., 2024). Some other bioactive components of essential oils are phenolic compounds (Wells, 2024). The mechanism of action of essential oils can be through respiration, circulation, and the central nervous system of the skin and respiratory tract. The respiratory system has a role in regulating memory, emotions, visceral activity, and brain functions such as alertness. The olfactory and neurotransmitter of the nervous system Orexin are found in the lateral regions of the neuronal hypothalamus such as the brainstem, basal forebrain, and hypothalamus (Zhong et al., 2019).

Some components of essential oils, including terpenes and terpenoids, may contribute to antioxidant activity (Pandey et al., 2024). Many studies have also shown that essential oils have anti-bacterial properties against various types of bacteria including zoonotic enteropathogens (Pezantes-Orellana et al., 2024). M.

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officinalis L. essential oil, which contains citral and citronelal, has effectiveness as an antiviral that inhibits HSV-2 replication (Shazadi et al., 2024). Essential oils also work as anti-inflammatories, such as essential oils from aloe vera (M'hamdi et al., 2024). In addition, essential oils from some plants contain several active components that can work on the central nervous system and reduce anxiety through various mechanisms. In animals, a decrease in anxiety can occur through the mechanism of neurogenesis and reduce neuronal apoptosis in the hippocampus, as well as inhibit the growth of immature dendrites so that it can reduce serum levels of BDNF (Brain Derived Neurotrophic Factor). Several other mechanisms can occur both cellularly and molecularly, including monoamine changes (Ayuob, 2017), inhibition of GABA and cytokines (Wang et al., 2018).

Anxiety is one of the most common health problems in the world that has huge consequences and decreases the quality of life (Rabbani et al., 2015). Anxiety causes increased vital signs, anorexia and sadness, decreased concentration, insomnia, weakens the immune system, inhibits wound healing, and interferes with physical activity (Sadeghi et al., 2020). Anxiety can occur due to stress. Stress can be a triggering factor that causes dysfunction of the neuroimmune-endocrine system. Several studies have shown that essential oils used from aromatherapy can reduce anxiety symptoms in humans and animals (Hsieh et al., 2024). Aromatherapy has also been widely used to improve quality of life and reduce psychological stress (Avola et al., 2024). This study was conducted to evaluate the bioactivity of essential oils as anxiolytic and the most effective essential oil widely used to reduce anxiety levels.

Method

This study employs a Systematic Literature Review (SLR) approach to identify and analyze the bioactivity of essential oils in alleviating anxiety symptoms (Sugiyono, 2022). The review was conducted using a structured and transparent process in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews. Relevant data were obtained from reputable academic databases, including PubMed, ScienceDirect, Scopus, SpringerLink, and Google Scholar. The articles reviewed were published within the last ten years and written in English. Selected studies focused on the anxiolytic effects of essential oils, either through preclinical studies (on animal models) or clinical trials (on human subjects), with attention to the mechanisms of action on the central nervous system (CNS). The data collection process involved several key stages. First, a keyword search was

performed using terms such as "essential oil," "anxiety," "bioactivity," "anxiolytic effect," "mechanism," "clinical trial," and "preclinical study." The inclusion criteria encompassed studies that specifically evaluated the anxiolytic effects of essential oils, while exclusion criteria involved studies lacking full-text access, irrelevance to the topic, or involving unrelated interventions.

Following the initial screening, relevant studies were reviewed in full, and data were extracted systematically. Findings were categorized according to the type of essential oil, type of study (preclinical or clinical), and the anxiety-related outcomes reported. The review synthesized patterns of anxiolytic activity, discussed the consistency and strength of the evidence, and evaluated potential pharmacological mechanisms, such as modulation of neurotransmitter systems. A summary table was created to compare and contrast the studies and facilitate interpretation of the results.

Result and Discussion

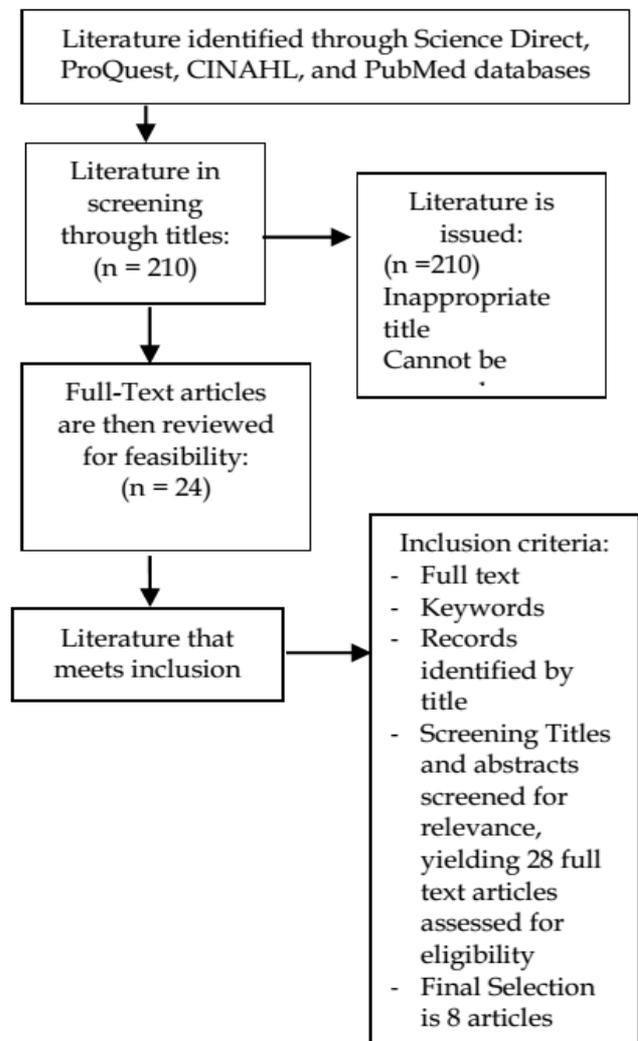


Figure 1. Flow diagram of the literature selection process flow

Agarwood Essential Oil

Agarwood is widely used for traditional medicine in countries such as China and Arabia (Dahham et al., 2015). The active components of agarwood observed in previous studies were benzyl acetone, α -gurjunene, and (+)-calarene (Takemoto et al., 2008). A preclinical study conducted by Wang et al. (2018), identifies that the chemical components of agarwood essential oil consist of 51.132% of 34 sesquiterpenes, 24.114% of 13 aromatic compounds, and 19.823% of 21 other compounds. This preclinical study tested the influence of agarwood essential oil as an anxiolytic. Adult male mice were divided into 7 groups with different treatments (no treatment, stress control, stress control with diazepam, paroxetine, and agarwood essential oil which were further divided into 3 groups (10/20/40 mg/kg). The mice were given medication and essential oils (depending on the group) injected intraperitoneally for 10 days. To assess the influence of essential oils, behavioral tests were used which included Elevated Plus Maze (EPM), Light Dark Exploration (LDE), Open Field (OF), Tail Suspension (TS), and Forced Swimming (FS). The results obtained showed a significant influence on the EPM, LDE, and OF tests. Meanwhile, antidepressant effects have been observed on TF and FS tests. This study shows that agarwood essential oil has an effect in reducing anxiety and depression, which is in line with previous research conducted by Wang et al. (2017) which observed the sedative effect of agarwood essential oil.

Bergamot Essential Oil

Bergamot essential oil comes from the bergamot plant which is a family of rutaceae that contains many beneficial substances. The most bergamot compounds identified by Rombolà et al. (2017). In preclinical studies, among others, it consists of 39.60% D-limonene, 31.09% linalyl acetate, 9.55% linalool. This preclinical study tested bergamot essential oil in mice with behavioral tests consisting of EPM, FS and OF tests. The animals were transferred to a clean room for 2 hours and given essential oils at a dose of 100/250/500 g/kg intraperitoneally. In the OF test, the 500 g/kg intervention showed a significant reduction in crossing, rearing and wall rearing. Bergamot essential oil at a dose of 250 or 500 g/kg also lowers grooming in animals. For the EPM test, the results of the increase in time spent and number of entries on open arms with a dose of 500 g/kg were obtained. For the FS test, the results were obtained of a decrease in swimming, an increase in immobility and the frequency of drowning recovering. Overall, the OF test and the EPM test showed that bergamot has an anxiolytic effect, which is in accordance with the research conducted by Bagetta et al. (2010) and Navarra et al. (2015) which states that bergamot oil has

neurobiological effects. However, the FS test in this study did not show any antidepressant effect on bergamot essential oil.

Cananga odorata Essential Oil (ylang-ylang)

Cananga odorata or also known as ylang oil contains a large number of derivatives such as Benzyl benzoate, linalool, benzyl alcohol, benzyl salicylate, geraniol, benzyl acetate, methyl benzoate which were identified in previous studies by Zhang et al. (2016). A preclinical study conducted by Zhang et al. (2018) investigating the effects of ylang oil on anxiety. The EPM test is used to analyze the behavior of animals. Rats were given 0.1/1/10% ylangana oil intraperitoneally after being stress-induced. The results of the EPM test, doses of 1 and 10% ylang oil can significantly increase the time spent and number of entries on the open arm, which suggests ylang oil has an anxiolytic effect. This is in accordance with research conducted by Zhang et al. (2016) which states that ylang oil has an anxiolytic effect.

Ocimum basilum Essential Oil

A preclinical study conducted by (Rabbani et al., 2015) has identified the chemical components of *Ocimum basilum*. Its main components are Methyl chavicol 42.8%, geraniol 13.0%, neral 12.2%, -caryophyllene 7.2%. This preclinical study tested the effect of *ocimum basilum* essential oil on reducing anxiety by conducting EPM and LA tests. Male mice were injected with essential oils at doses of 150 and 200 mg/kg intraperitoneally. The results obtained on EPM, a dose of 200 mg/kg of essential oil increased the number of entries in the open arm, but not significantly. A significant decrease in mouse motor activity was obtained in the LA test on essential oils at a dose of 200 mg/kg. These results show that *Ocimum basilicum* has a sedative effect.

Lavender Essential Oil

A study conducted by Shellie et al. (2002) has identified the active compounds of Lavender essential oil extracted from *Lavandula angustifolia*. The active compounds obtained include Linalool, and several other components such as -pinene, o-cymene, -ocimene, -ocimene, allo-ocimene, -terpineol, camphene, -3-Carene, -terpinene, terpinen-4-ol, Caryophyllene, -humulene. Lavender essential oil is widely used to treat anxiety. Preclinical studies conducted by Sánchez-Vidaña et al. (2019) examined twenty-four adult mice divided into four groups, namely the control group, the corticosterone group, the lavender essential oil administered by inhalation, and the combination of lavender essential oil and corticosterone. Treatment was given for 14 days, and behavioral tests (FS and SI) were performed on the last day of treatment. The results

showed that lavender essential oil reduced the time spent floating in the FS test, which showed that lavender essential oil had an antidepressant effect, which was in line with the research conducted by Cavanagh et al. (2002), Greenberg et al. (2017), and Perry et al. (2012) which states that lavender essential oil has an antidepressant effect. However, the SI test did not show any aggressive behavior from the animal. A clinical study conducted by Beyliklioğlu et al. (2019) examined lavender essential oil in patients before breast surgery using the STAI test. The study showed a significant decrease in the average test score showing that lavender essential oil can reduce patients' anxiety levels before breast surgery.

Another clinical study conducted by Karadag et al. (2017) regarding the effect of lavender essential oil on sleep quality and anxiety of coronary patients in the ICU, showing a significant decrease in PSQI and BAI scores from pretest to posttest. which shows a decrease in anxiety levels. In other words, lavender essential oil can lower anxiety levels and improve sleep quality for coronary patients in the ICU. Other clinical research conducted by Özkaraman et al. (2018). It also showed the effects of lavender essential oil on the sleep quality and anxiety of patients undergoing chemotherapy. Data observed from PSQI and STAI showed a significant decrease in scores indicating a decrease in anxiety levels and an improvement in the sleep quality of patients undergoing chemotherapy. Other clinical research has also been conducted by Karan (2019) which investigated the effect of lavender essential oil on wisdom teeth extraction patients under the influence of local anesthesia. In vital signs and anxiety levels, there was a significant decrease in MDAS and STAI tests which showed a decrease in anxiety levels accompanied by a decrease in diastolic pressure.

Other clinical research conducted by Rajai et al. (2016), regarding the effect of lavender essential oil on patients undergoing coronary surgery after graft bypass surgery tested with the DAAS test, there was a significant decrease in anxiety tests showing a decrease in anxiety levels and a decrease in heart rate. This suggests that anxiety levels are lower in patients who are given lavender essential oil. The effects of essential oils to reduce anxiety were also observed in clinical studies conducted by Abbaszadeh et al. (2020) using VAS tests in patients with bone marrow biopsy. Essential oils can significantly lower the average value on VAS tests. When compared between the control group and the group tested, it showed that lavender essential oil could lower anxiety levels.

Nectandra Grandiflora Essential Oil

Studies that have been conducted by Garlet et al. (2017), it has been observed that (+)-dehydrofukinone

(DHF), dehydrofukinone epoxide (DFX), eremophil-11-en-10-ol (ERM), selene-11-en-4- α -ol (SEL) are the main components of *Nectandra grandiflora*. Preclinical research conducted by Garlet et al. (2019) has investigated the effects of *Nectandra grandiflora* on anxiety. Mice were given essential oils at doses of 10, 30 and 100 mg/kg orally. The tests used consisted of EPM and OF tests. The results obtained showed that *nectandra grandiflora* gave positive results in the EPM test parameters (significantly increasing the open arms and number of entries) and also in the OF test (significantly increasing the time spent on the central part). All tests showed that *nectandra grandiflora* had an anxiolytic effect.

Cinnamo Essential

A preclinical study conducted by Sohrabi et al. (2017) have identified the chemical components of Cinnamon Essential Oil. The main components of cinnamon include 87.32% Trans-cinnamaldehyde, 3.31% beta-tumerone, 2.34% o-cinnamaldehyde diethyl acetal, and 1.88% o-methoxycinnamaldehyde. This preclinical study evaluated the antidepressant and anxiolytic effects of cinnamon essential oil. The behavioral tests used consisted of FS, TS, EPM, and OF tests. Treatment is given in both acute and sub-acute ways. Animals were injected intraperitoneally with three doses of essential oils (0.5/1/2 mg/kg). For sub-acute treatment, animals are given injection treatment for 14 days. The results of the FS test showed a significant decrease in immobility. In the TS test, essential oils significantly reduce time spent. In the EPM test all parameters showed significant positive results (increased time spent and number of entries on open arms). However, in the OF test, there was no significant decrease. Thus, FS, TS, and EPM show that cinnamon essential oils have an anxiolytic effect.

Rose Essential Oil (Comparison with Lavender Essential Oil)

Roses can affect the central nervous system including the brain because they contain citronellol and phenethyl alcohol (2-phenylethanol) (Umezu et al., 2002). Clinical research conducted by Abbasjahromi et al. (2020) to 90 female patients undergoing Caesarean section with spinal anesthesia using a questionnaire consisting of individual characteristics, STAI and VAS tests for data collection. The data obtained was analyzed using SPSS. This study compared the effects of lavender and rose essential oils. The results showed that both lavender and rose essential oils did not show a significant difference in STAI values. The results showed that lavender and rose essential oils could not reduce anxiety levels in the study. However, the VAS test showed that the level of pain was reduced in both groups with a significant decrease in values. But the group with rose oil had a greater effect. In conclusion,

rose essential oil is more effective in reducing pain compared to lavender essential oil (Sukmawati, 2019).

Lemon Essential Oil

A clinical study conducted by Johnson (2019), surveyed 31 nursing students. Students are divided into two groups. The essential oil is dripped 8-9 drops into a cotton swab and the group can use aromatherapy when they experience symptoms of anxiety. Data collection was conducted using CTAS test questionnaires and data analysis using SPSS. Results obtained from 31 students divided into 2 groups, i.e. 16 students in the control group and 15 students in the test group, showed no significant change in the mean CTAS score between the pretest and posttest in the control group and the test group. There was a decrease in the mean CTAS score in the control group from pretest to posttest, but it was not significant. A decrease in the average score of CTAS also occurred in the test group which also did not provide a significant decrease in score. This study states that lemon essential oil does not provide a significant decrease in CTAS scores for nursing students from pretest to posttest.

Origanum Majorana Essential Oil -Citrus Sinensis

A clinical study conducted by Son et al. (2019) use double-blind randomized controlled trial. This study was conducted on 98 second-year nursing students. The subjects were divided into 3 groups, 32 students in the aromatherapy group, 32 students in the music therapy group and 34 students in the combination group between aromatherapy and music therapy. Inhalation of 3 drops of essential oil was given to each subject. The music therapy used is Beethoven's moonlight sonata. Data collection was carried out by distributing questionnaires. Students inhale aromatherapy for 20 minutes for the aromatherapy group. For the music therapy group, students listen to music for 20 minutes. The combination group did both, both inhaling aromatherapy and listening to music for 20 minutes. Data collection was carried out by distributing questionnaires with anxiety tests, STAI, stress tests calculated with numeric rating scores (NRS) and nurse skills. Data analysis using SPSS. The results obtained in this study stated that there was no significant difference between the three groups on each test before the intervention. After the intervention was carried out, the results were obtained with significant differences between the three groups in each test. The combination therapy group between aromatherapy and music therapy showed a significant decrease in anxiety tests, STAI, and stress tests so that it could improve nurses' skills. No significant differences were obtained from the groups given aromatherapy or music therapy alone. In other words, the combination of aromatherapy and

music therapy is effective in lowering stress levels in nursing students.

Orange Essential Oil

A clinical study conducted by Rashidi-Fakari et al. (2015) The results obtained showed that the level of anxiety in both groups decreased after the intervention. However, a larger decline occurred in the test group. A decrease in heart rate and diastolic blood pressure was also obtained in the test group patients. This study states that orange aromatherapy can reduce anxiety levels, diastolic blood pressure and heart rate. It can be said that citrus astiri oil can serve to lower anxiety levels during childbirth.

Chammomile-lavender Essential Oil

Chamomile is one of the plants that is widely used as an essential oil. Chamomile increases cortisol secretion and lowers anxiety levels (Keefe et al., 2018). A clinical study conducted by Zamanifar et al. (2020) using a randomized and a double-blind clinical trial of 120 nurses. Nurses were divided into 4 groups with different interventions. The first group was the chamomile and lavender aromatherapy group, the second group was the music therapy group, the third group was the combination group of aromatherapy and music therapy, and the last group was the control group. Data collection was conducted using a questionnaire containing patient information and the Beck Anxiety Inventory Test (BAI). The data obtained was analyzed with SPSS. In the aromatherapy group, the nurse was given 3 drops of aromatherapy. In group music therapy, nurses listen to their favorite music for 20 minutes. In the combination group, the nurses were given aromatherapy while listening to music. And no intervention was given to the control group. The results obtained from this study stated that there was no significant difference between the four groups before the intervention. However, there were significant differences between the four post-intervention groups. There was a significant decrease in scores in the aromatherapy group, music therapy, and the combination of aromatherapy with music therapy compared to the control group. This study states that aromatherapy, music therapy and a combination of aromatherapy and music therapy can lower anxiety levels in nurses.

Mechanism of Action

Anxiety is a disease of the central nervous system that can occur due to stress. The effects of stress can lead to dysfunction of the neuroimmune-endocrine system. Another pathway of stress induction can be through hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis can be affected by many factors, such as cytokines and nitric oxide (NO).

Cytokines, which are generally secreted by immune system cells, can also be synthesized and secreted by non-immune cells for the purpose of signaling neuroimmune cells. Proinflammatory cytokines, including interleukin-1 α (IL-1 α), IL-1 β , and IL-6, are secreted in all components of the HPA axis and affect the secretion of corticotropin-releasing factor (CRF) from the hypothalamus, adrenocorticotropic hormone (ACTH) from the pituitary, and glucocorticoids from the adrenal cortex. NO is a neurotransmitter produced by neuronal NO synthase (nNOS) and inducible NO synthase (iNOS) in the brain and is involved in the regulation of HPA axis, especially in response to increased CRF. Furthermore, CRF is distributed in the central nervous system (CNS) and has a role in regulating the main physiological of the stress response (Sanders & Nemeroff, 2016).

Research conducted by (Wang et al., 2018) has tested that agarwood essential oil can significantly inhibit the concentrations of IL-1 α , IL-1 β , and IL-6. RT-PCR and Western Blot Experiment tests stated that the anxiolytic and antidepressant effects on agarwood occurred due to the inhibition of CRF through the HPA axis hyperactivity pathway. Furthermore, the research conducted by Zhang et al. (2018) investigated that the influence of ylang oil for anxiolytics and antidepressants occurred due to a reduction in the phosphorylation level of ERK1/2/ (Extracellular signal-regulated kinase) and also a decrease in the regulation of the CREB phosphorus pathway (cAMP response element-binding protein) in the hippocampal pathway and relevant to the serotonin system. Other research that has been conducted by López et al. (2017) states that the anxiolytic and antidepressant effects of lavender essential oil may be due to antagonism on NMDA receptors (n-methyl-D-aspartate) and inhibition of SERT (transporter serotonin). Furthermore, the research conducted by Garlet et al. (2019), A study conducted to investigate the anxiolytic effects of nectandra grandiflora says that positive modulation of GABA α receptors and inhibition of neuronal calcium influx may produce anxiolytic effects in mice.

Conclusion

Based on the research results and discussions, it can be concluded that essential oils show various bioactivities that affect the CNS, supporting their role as potential anxiolytic agents.

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Author Contributions

Conceptualization, H.P and S.; methodology, H.P and S.; software, H.P and S.; validation, H.P and S.; formal analysis, H.P and S.; investigation H.P and S.; resources, H.P and S.; data curation, H.P and S.; writing—original draft preparation H.P and S.; writing—review and editing, H.P and S.; visualization, H.P and S.; supervision, H.P and S.; project administration, H.P and S.; funding acquisition, H.P and S.

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Conflicts of Interest

The authors declare no conflict of interest.

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