

Lavender Used in CNS Disorders

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Abstract: Lavender is one of the important plant belonging to family lamiaceae this species are widely distributed and cultivated in itly, france, spain. it is also known as important aromatic and medicinal herb it produce essential oil the oil contains hundred of chemicals compounds such as linalool, linalyl acetate, lavandulyl acetate. It show effective improvement in CNS disorders like alzheimer, depression, epilepsy, anxiety, migraine.

Keywords: lavender, essential oil, disorders

I. INTRODUCTION

Lavender is one of the important plant belonging to family lamiaceae .this species are widely distributed and cultivated in itly,france,spain.it is also known as important aromatic and medicinal herb it produce essential oil the oil contains hundred of chemicals compounds such as linalool,linalyl acetate,lavandulyl acetate. The Lavandula augustifolia Mill. specie is well known as important aromatic and medicinal herb that is used in traditional and folk medicines for its importance in the treatment of several gastrointestinal, rheumatic and nervous disorders this plant have high antioxidant activity,antimicrobial agent.it avt against many fungal species,anti inflammatory activity,painful relief effect,wound healing effect and insecticide agent.it is also used an ingredient in both salts and washing agent. [1-4]



Fig. 1: The whole plant (Lavandula angustifolia)



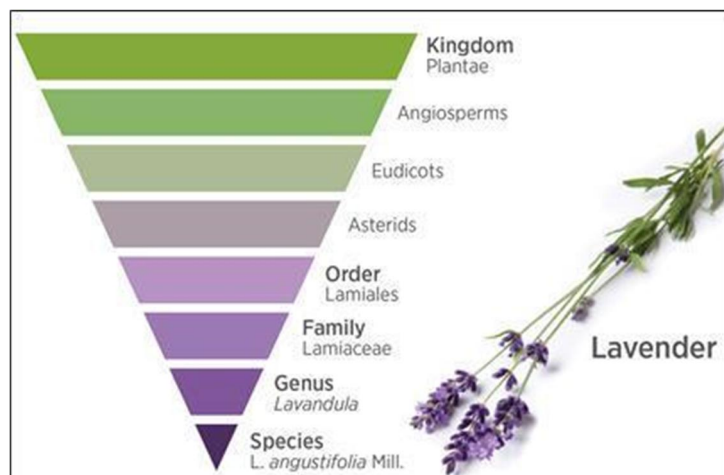


Fig.2: The classification of Lavender

CNS(central nervous system) disorders remain leading cause of disability .in this prolonged care than almost diseases .cns diseases is mostly related to brain .cns diseases is challenging because avariety of obstacles often impede drug delivery to the brain and spinal cord.[5]

2. Effects of lavender on CNS disorders:

• Alzheimer's diseases:

Alzheimer's disease (AD) is a neurodegenerative disease. It is characterized by progressive cognitive deterioration with declining activities of daily living and behavioral changes. It is the most common type of pre-senile and senile dementia. Guided by World Health Organization (WHO), 5% of men and 6% of woman of above the age of 60 years are affected with Alzheimer's type dementia worldwide.

The clinical manifestation of Alzheimer disease (AD) is dementia that typically begins with the subtle and poorly recognized failure of memory and slowly becomes more severe and, eventually, incapacitating.[6]

Lavender essential oil is a well-known mixture mostly extracted from *L. angustifolia*. LO and its major component, linalool, have shown multiple bioactivities especially for AD diseases[7- 8] Silexan is a essential oil produced from fresh *Lavandula angustifolia* flowers by steam distillation. Silexan contains a quality selected, well-defined preparation from *Lavandula angustifolia* in a immediate release capsule that contains 80 mg of essential oil. Silexan acts the GABAA receptors, and pre-clinical data have suggested that it may have anxiolytic and antidepressant potential.

Behavioral recovery following chronic exposure to essential oils extracted from *Lavandula angustifolia* ssp. *angustifolia* Mill. and *Lavandula hybrida* Rev. cultivated in Romania, using scopolamine-induced dementia rat model, was studied.

The main components in both analyzed samples, *Lavandula angustifolia* and *Lavandula hybrida*, were the linalool (28.0% and 21.5%, respectively) and linalyl acetate (17% and 22.5%, respectively) followed by terpinen-4-ol (3.3% and 16.7%), lavandulyl acetate (8.3% and 8.4%). *Lavandula angustifolia* and *Lavandula hybrida* in scopolamine-treated rats not increase the percentage of spontaneous alternation.

This result suggests that lavender essential oils used in this study does not display any improvement effect on acquisition of the short term-memory of the scopolamine treated rats within Y-maze task. In radial arm maze-task, the scopolamine-treated groups exposed to *Lavandula angustifolia* and *Lavandula hybrida* essential oils showed significant decrease of the number of working memory errors and increase in time taken to consume all five baits compared to control group, during 7 days training. These results strongly suggest positive effects of the lavender oils on short-term memory. [9]



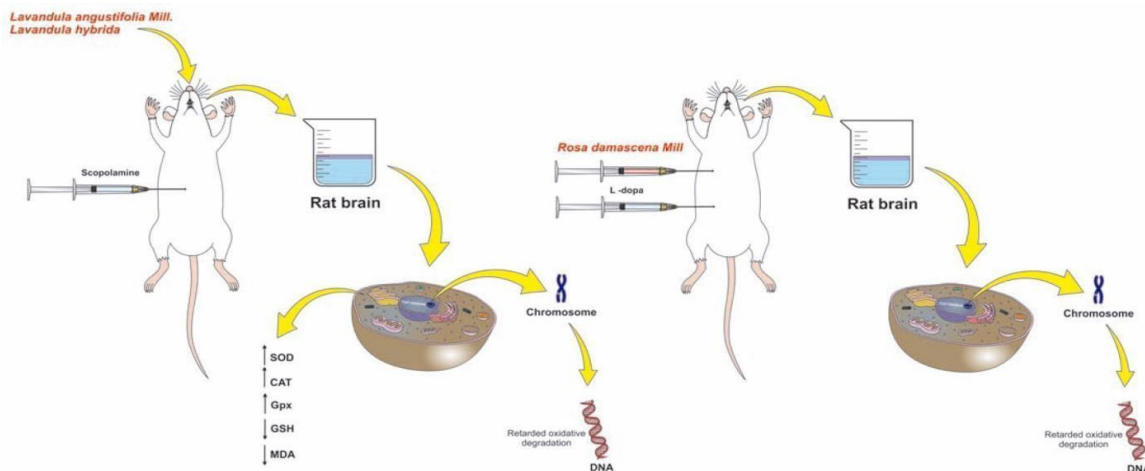


Fig. 3: Mechanisms of action proposed for *Lavandula angustifolia* Mill. EOs *Lavandula hybrida* Rev. and *Rosa Damascena* Mill. and in in vivo models for neurological disorders[10]

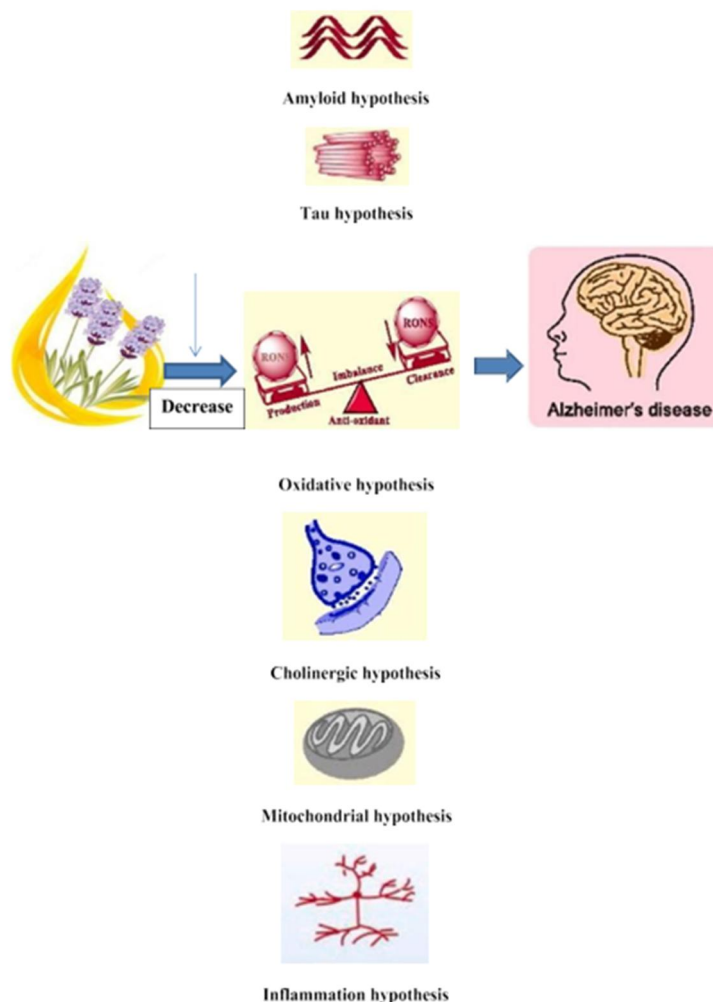


Fig. 4: Pathophysiology of Alzheimer's Disease (AD); antioxidant, anti- inflammatory, and anti-cholinergic effects of essential oils.[15]



• **Depression:**

Depression is a mental illness that significantly impacts an individual's quality of life and is characterized by persistent feelings of sadness, fatigue, and disinterest in everyday tasks [11]. It is considered a common but serious health condition, affecting millions of individuals all over the world. According to the World Health Organization (WHO), nearly about 300 million people worldwide have depression [12]. The onset of depression commonly occurs in the mid-20s, and women have nearly twice the chance of experiencing depression compared to men [13]

In this respect, numerous pharmacological and non-pharmacological therapies are offered for depression improvement. Concerning the pharmacological therapies, it seems that many drugs play significant roles in treating psychological disorders; however, with respect to the presence of many complaints regarding the uselessness of these drugs for all patients, along with the emergence of diverse side effects and tolerance (if they are used in the long-run), numerous researchers have noticed using non-pharmacological therapies.

Several studies have addressed the positive effect of some non-pharmacological therapies, including art therapy, music, and aromatherapy, on the improvement in depression and anxiety. In the meantime, aromatherapy, is a non-pharmacological method, has been exploited in many studies owing to its hazardless and convenient usage. Aromatherapy employs the fragrant oils extracted from flowers and herbs to treat varying diseases. Essential oils can be used by inhaling, taking bath, or during massages. Lavender is of those herbs that are used in aromatherapy. This herb is from the lamiaceae family with the scientific name of *lavandula angustifolia*.

Many studies have addressed the anti-pain, antianxiety and anti-depressant, and sleep improvement effects. Also, some researchers have believed that lavender exerts its psychological effects through the effects on the limbic system, especially the amygdala and hippocampus. Mechanism of this plant on the cell surface is not completely known, but it has been reported that this plant probably had a similar function to benzodiazepines and increased GABA (gamma aminobutyric acid) in the amygdala.

On the other hand, the review of the available databases showed that although some studies have reported the positive effects of aromatherapy with lavender on depression, but some others have reported reverse results.

Thus, considering the presence of contradictions in this field, lavender's application to improving depression is still being argued. Hence, to access many precise and comprehensive evidence, this study reviewed the effect of aromatherapy with lavender on depression.[14]

Five articles evaluated the action of orally consumed lavender on depression as the main outcome measure. One study evaluated the action of lavender in the form of Silexan (an immediate release capsule containing *L. angustifolia* essential oil) on patients with mixed anxiety and depression (MADD). The results of the study conducted by Kasper et.al., on patients with MADD showed statistically significant reduction in depression and anxiety scores later 4 weeks, and managed to maintain positive effects at week 10 compared to the placebo group.

Also, in an 8-week study carried out on patients with mild to moderate depression, there is a significant reduction in depression scores in the group receiving oral lavender capsules comparable with the group consuming fluoxetine. Also, in line with the aforementioned studies, antidepressant effects compared to control groups. While Chen et al. study, on postpartum woman with sleep disturbances, resulted in reduced depression scores at week 2 post intervention with no significant sustained effects at week 4 of follow up.[16]



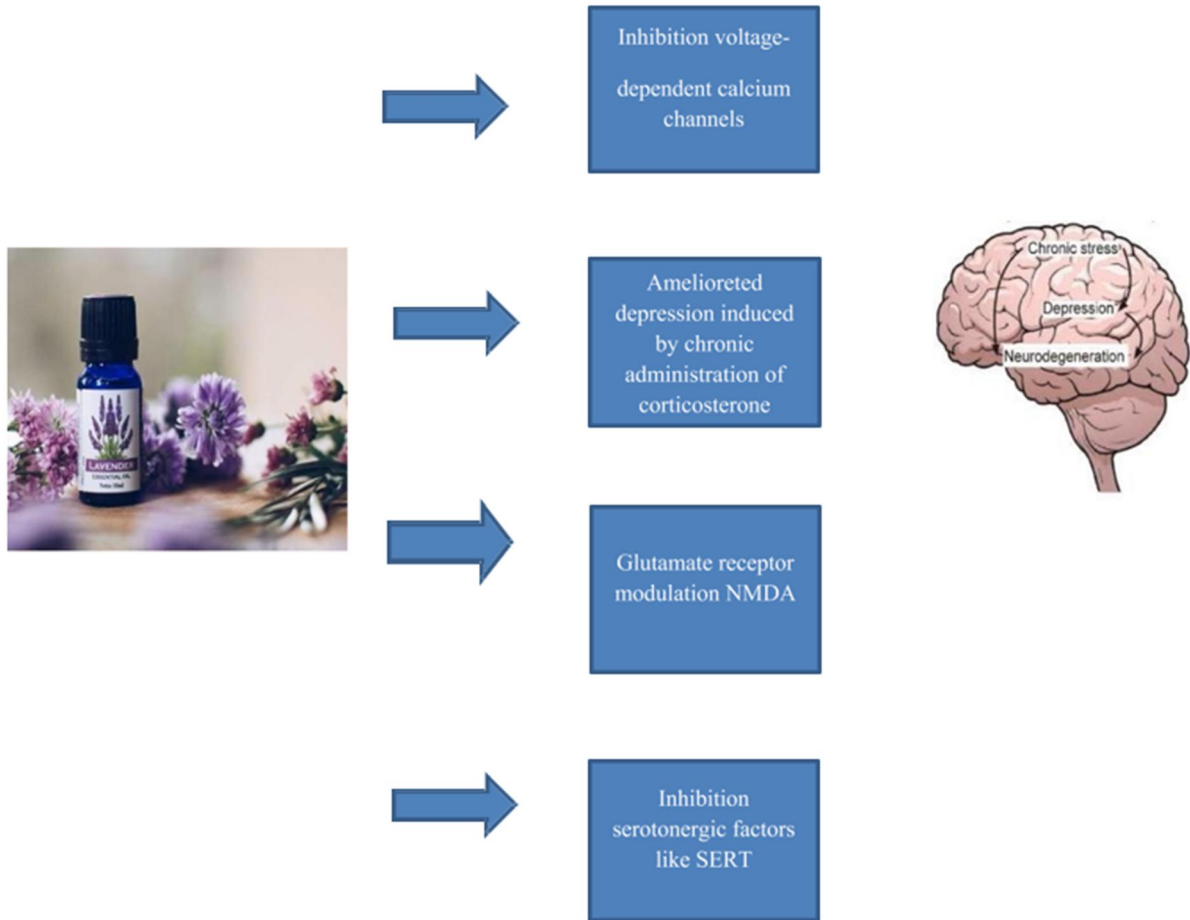


Fig.5 Aromatherapy by lavender treats depression by inhibiting voltage-dependent calcium channels and serotonergic factors and modulating NMDA receptors.[15]

• Epilepsy:

About 1% of the population is affected by epilepsy, making it the second most common neurological disease after a stroke.[17] upto 50 million people worldwide have epilepsy, and 90% of them come from developing countries.[18] The perception of epilepsy has improved in several respects in the recent years. It is a common chronic neurological disease in which the balance between brain excitability and inhibition inclines uncontrolled excitability and is characterized by recurrent unprovoked epileptic seizures.[19-21] Now there is clear evidence that there are clear differences in pathophysiology between immature and mature brains and the effects of strokes.

It is a collection of different forms of epileptic seizures, which widely in frequency, appearance, cause and management of consequences.[22] Seizures are associated with the characteristic signs and symptoms of abnormal neuronal activity, excessive or synchronous in the brain.[23] Epileptic seizures repeatedly cause a temporary loss of consciousness, leave the patient at risk of physical harm and often interfere with education and employment.

Epilepsy is much likely to occur in young children or people over 65 years of age; however, it can occur at any time. Epilepsy is not a single disease, but a syndrome with very different symptoms, involving episodic abnormal electrical activity in the brain.[24] Around 20–30% of patients with epilepsy have drug-resistant seizures . Also, seizure recurrence is observed in 5% of people worldwide, and 35% of people have uncontrolled epilepsy .

Proper diagnosis of epilepsy syndrome is needed, and when refractory epilepsy is confirmed, surgery is regarded for patients. Surgery is used selectively for patients with treatment-resistant focal seizures .



Other treatments for epilepsy are underused vagal nerve stimulation or closed-loop cortical stimulation . New-generation anti-epileptic drugs (AEDs) have side effects, including psychological complications, like depression, anxiety, and cognitive deficits . However, these AEDs have fewer side effects in comparison with older-generation AEDs .

Natural products used in traditional medicine are powerful sources of new AEDs. They have been primary treatments for patients with epilepsy because of their availability. Also, Ekstein in 2010, confirmed that new drug therapies are more cost-effective for patients . Lifestyle changes can prevent seizure precipitation in teenagers with idiopathic generalized epilepsy .

Powerful anticonvulsive effects of lavender and other essential oils high in linalool have been demonstrated in animal models of seizure . Linalool is known as a monoterpene alcohol that strengthens GABAA function in mammalian electrophysiology experiments.

Linalool oxide, linalyl acetate, 8-oxo linalyl acetate, 8-carboxy linalyl acetate, and 8- oxo linalool are linalool derivatives and metabolites. Also, the metabolites play a role in GABA-A function .

In snail neurons, linalool inhibits sodium channels and increases potassium currents (Fig. 6). The lower concentration of linalool has a suppressive effect on spontaneous activity and PTZ-induced epileptiform activity. A higher concentration of linalool can Pproduce epileptiform activities, reversible by calcium channel blockers . The administration of Cinnamosma madagascariensis (0.4 and 0.8 mL/kg bw), Zhumeria majdae, and Citrus aurantium blossom oils has been found to decrease convulsions in animals treated with PTZ. Furthermore, these oils have been shown to increase latency and survival .

Inhaled lavender essential oil (1 mL) administrated 15 min before pentylenetetrazole (PTZ) treatment, could prevent all convulsions in 100% of the animals leading to a 100% survival rate. The animals of the control group receiving PTZ were found with seizures and at this dose, there was a 100% mortality rate .

Lavender increases GABAA function and potassium current. Inhaled lavender essential oil before PTZ treatment could prevent all convulsions in animals.[15]

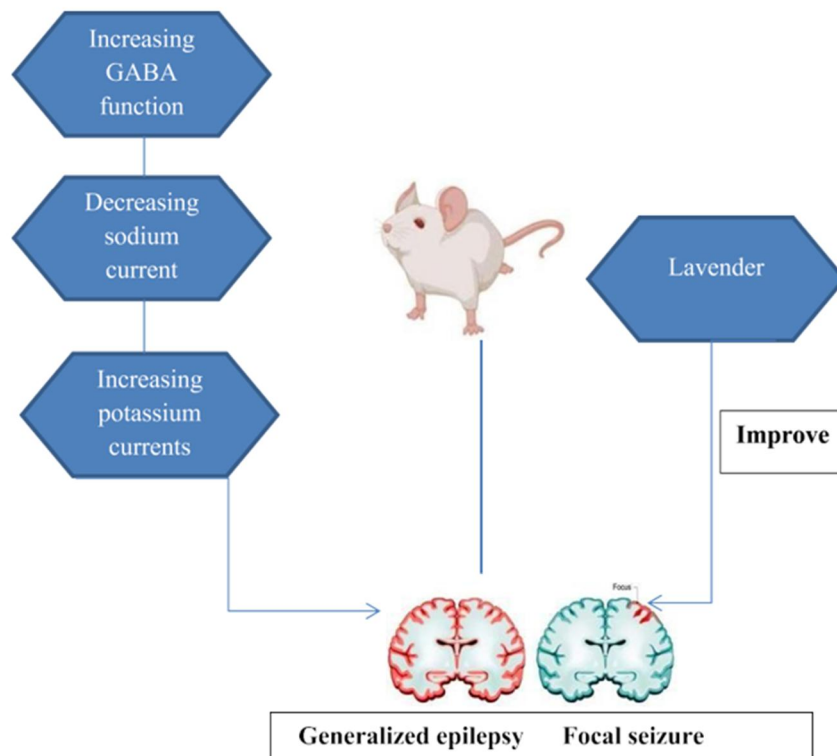


Fig. 6 Lavender exerts antiepileptic effects by increasing potassium current and GABA function and reducing sodium current.



• Anxiety:

Anxiety disorders are the most prevalent psychiatric disorders (with a current worldwide prevalence of 7.3% [4.8%-10.9%]—Stein et al, in this issue p 127). Among them, certain phobias are the most common, with a prevalence of 10.3%, then panic disorder (with or without agoraphobia) is the next most common with a prevalence of 6.0%, followed by social phobia (2.7%) and generalized anxiety disorder (2.2%). Evidence is lacking as to whether these disorders have become more prevalent in recent decades.

Generally speaking, women are more prone to develop emotional disorders with an onset at adolescence; they are 1.5 to 2 times more likely than men to have an anxiety disorder [25-26] There is a high comorbidity between anxiety (especially generalized anxiety disorders or panic disorders) and depressive disorders. Additionally, anxiety disorders are often associated, which renders treatment even more complex for nonspecialists. As a result, anxiety disorders often remain underdiagnosed and undertreated in primary care.[27]

Different types of anxiety disorders are generalized anxiety disorder (GAD), social anxiety disorder (SAD), phobias, posttraumatic stress disorder (PTSD), obsessive- compulsive disorder (OCD), and panic disorder (PD) . In addition to blood pressure and heart rate, including cortisol and salivary chromogranin A (CgA), are used to assess anxiety . Anxiety is handled with psychotherapy and medication but patients with more severe anxiety disorders may develop depression and physical illnesses and are prone to substance abuse .

Anxiety medications, such as benzodiazepines and selective serotonin reuptake inhibitors (SSRIs) have side effects, like amnesia, sedation, and diminished concentration .

Therefore, there is a need for more effective drugs with fewer side effect. Also, even patients using drugs, psychotherapy, and brain stimulation therapies show little or no improvement, which indicates the need for newer methods to treat this disorder.

Based on studies performed on normal people and people with anxiety, some chemicals and neurotransmitters have been shown to be involved in anxiety . Neurotransmitters involved in this disorder include serotonin (5-HT), norepinephrine (NE), GABA, dopamine (DA), histamine (H), and Ach .

The sedative effects of lavender oil inhalation have been significantly studied on animals . The acute effects of hydro-alcoholic extract of lavender (25, 50, or 100 mg/kg, intraperitoneally) on anxiety-like behavior in rats were indicated using an elevated plus-maze (EPM) test. Lavender extract showed an anxiolytic activity similar to that of low-dose diazepam .

Various studies have shown the effect of lavender oil in the form of creams and perfumes on the treatment of anxiety and its effect on anxiety is similar to chlordiazepoxide and is more effective than lorazepam . In different studies, the positive effects of lavender using various methods, such as massage and inhalation during labor, have been shown . Siloxane is a standardized form of lavender essential oil collected from the distillation of the fresh *L. angustifolia* Miller flowers .

Silexan acts through the potent inhibition of voltage-dependent calcium channels in brain areas, such as the hippocampal neurons . The Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) has accepted the use of oral lavender essential oil for the treatment of mental stress, and it is licensed in 14 countries around the world. Lavender oil has been shown to inhibit voltage-dependent calcium channels (VOCCs) in synaptosomes, primary hippocampal neurons, and stably overexpressing cell lines in a similar range as pregabalin. This inhibition is mainly mediated via N-type and P/Q-type VOCCs. However, further investigations are needed to assess the long-term effects of lavender use . Lavender is one of the most effective and healthy choice for treating anxiety . Essential oils of lavender increased happiness hormones even by ten times .

L. angustifolia (also named *L. vera* or *L. officinalis*), which is the most widely used species of lavender, has main compounds, including linalyl acetate and linalool. These compounds are responsible for the medicinal effects of the plant, including its sedative effects . Linalool in lavender has an proscriptive effect on the GABA-A receptors, and autonomic and limbic systems that lower blood pressure .

Lavender essential oils exert their calming effect through various proposed mechanisms, such as GABA receptor inhibition, the reaction of linalool with glutamatergic NMDA receptors, inhibition of serotonin transporter (SERT), antagonizing the NMDA receptor, inhibiting tension- dependent calcium channels, and affecting the 5HT-1A receptor in specific brain areas, such as temporal gyrus .



The results of a study showed that the interventions using music therapy and aromatherapy with chamomile-lavender essential oil could decrease the anxiety of nurses in clinical settings . In 2021, the positive effects of lavender aromatherapy and Citrus aurantium aromatherapy on decreasing the anxiety of patients were documented . Inhalation with 1.5% lavender and chamomile essential oils for 30 nights decreased depression, anxiety, and stress levels in community-dwelling older adults .

Aromatherapy with inhaled lavender essential oil and breathing exercises can be considered an effective intervention to reduce electroconvulsive therapy (ECT)-related anxiety in depressed patients . Aromatherapy with lavender treated anxiety and depression in patients. This herb has a sedative effect through the inhibition of GABA receptor, inhibition of SERT, antagonizing the NMDA receptors, inhibition of tension-dependent calcium channels, and affecting the 5HT-1A receptors in specific brain areas, such as temporal gyrus.[15]

• Migraine:

Migraine is a severe and complex neurovascular disease that affects 16% of the population. It starts in childhood and increases between the ages of 22 and 55 years, affecting females more than males (3:1) with a family history of migraine. It is a chronic condition with occasional symptoms and is ranked as the sixth most debilitate disease in the world and the most disabling neurological disorder by the World Health Organization. Financially, it has a significant effect on economies globally which costs US\$19.6 billion annually.[28]

This neurological disorder is consist with hormonal changes. After puberty, the incidence of migraine increases, whereas its prevalence decreases during pregnancy [29-30]. There is an increase in plasma levels of calcitonin gene-related peptide (CGRP), a strong vasodilator and marker of trigeminal inflammation, in patients with migraine [31].

Different factors, like nutritional habits, hormonal diseases, digestive disorders, autoimmune disorders, structural imbalances, mental stress, and lifestyle are involved in the pathology of migraine [32]. Venlafaxine, beta-blockers, valproate, topiramate, amitriptyline, flunarizine, magnesium, gabapentin, and botulinum toxin type A are used to treated the migraine [33]. The headache frequency and severity are prevented by supplements and medicinal herbs [34].

The effectiveness of traditional medicine and medicinal herbs has been demonstrated worldwide [35]. Pharmacotherapy, massage therapy, acupuncture therapy, and aromatherapy are used for the treatment of migraine. The best treatment for relieving the symptoms of the disease is aromatherapy. Traditional Chinese Medicine Aromatherapy is indicates the efficacy of aromatic plants and their application in the treatment of different diseases [36].

Based on a single-blind study assessing the effectiveness of the topical usage of lavender oil on migraine, 47 patients with migraine at the beginning of attacks, were administrated with two to three drops of a placebo solution (liquid paraffin) or lavender oil apply onto their upper lip followed by inhalation the vapor for 15 min [37]. The procedure was employed for six consecutive migraine attacks.

According to the results obtained from the 129 migraine attacks through the research period, the lavender group had a 3.6-point decrease in rating severity (on a 10-point rating scale), which was more compared to the 1.6-point decrease in rating severity in the placebo group (obtained data from 68 attacks). The lavender group (71%) also showed a higher percentage of total or partial responders than the placebo group (47%).

In addition, 74% of the subjects in the lavender group showed an improvement in migraine symptoms (vomiting, nausea, photophobia, and phonophobia) in comparison with only 58% in the placebo group. In animal models, lavender caused a reduction in inflammation and neuropathic pain by affecting peripheral and central opioid and cannabinoid 2 receptors [38].

In another animal research, after renal ischemia/reperfusion injury, lavender oil significantly improved antioxidant enzyme activity, decreased lipid peroxidation, and markedly reduced concentration of the cytokines, tumor necrosis factor- α , and interleukin-1 β [39]. Also, the effect of lavender as a prophylactic therapy was investigated for migraine in a randomized controlled clinical trial. In a three-month trial, the group that received lavender showed a decrease in the frequency and severity of migraine attacks. Additionally, lavender oil was found to be effective in preventing migraines [35]. Studies on human cell lines have indicated the efficacy of estrogenic and antiandrogenic properties of the lavender oil and it can be used in adults with an obvious allergy to lavender [40].



Linalyl acetate (LA), available in lavender oil, exerts its anti-inflammatory effects by affecting the NF- κ B activation. According to the results reported by Koto et al. (2006), rabbit carotid arteries were dilated by lavender [41]. Arginine nitrate, as a nitric oxide synthase (NOS) inhibitor, and 1H-[1,2,4] oxadiazole [4,3- α] quinoxaline-1-one, as the guanylyl cyclase inhibitor, have relaxation effects [36].

Shin et al. (2018) also found that in diabetic rats, the isolated aortic vasodilation caused by stress from ACh increased following an intraperitoneal injection of a low concentration of LA [42] (Fig. 7). In addition, by an increase in the concentration of LA, ACh-related vasodilation approximately reached the control levels. Accordingly, LA may have an anti-migraine effect via inhibiting neurogenic inflammation and balancing vasomotor impairments. Therefore, more studies on plant essential oils are needed to develop novel anti-migraine agents [36].

A study found that using a 1:1 combination of essential oils from *Lavandula angustifolia* and *Citrus bergamia* (0.1 mL of 100% *Lavandula angustifolia* +0.1 mL of 100% *Citrus bergamia*) for 28 days effectively improved the quality of life, particularly among nurses working in emergency and critical care units during the intervention period. Lavender oil significantly improved antioxidant enzyme activity, decrease lipid peroxidation, decreased the concentration of the cytokines, tumor necrosis factor- α , and interleukin-1 β , and improved migraine in human, animal, and cell studies.[43]

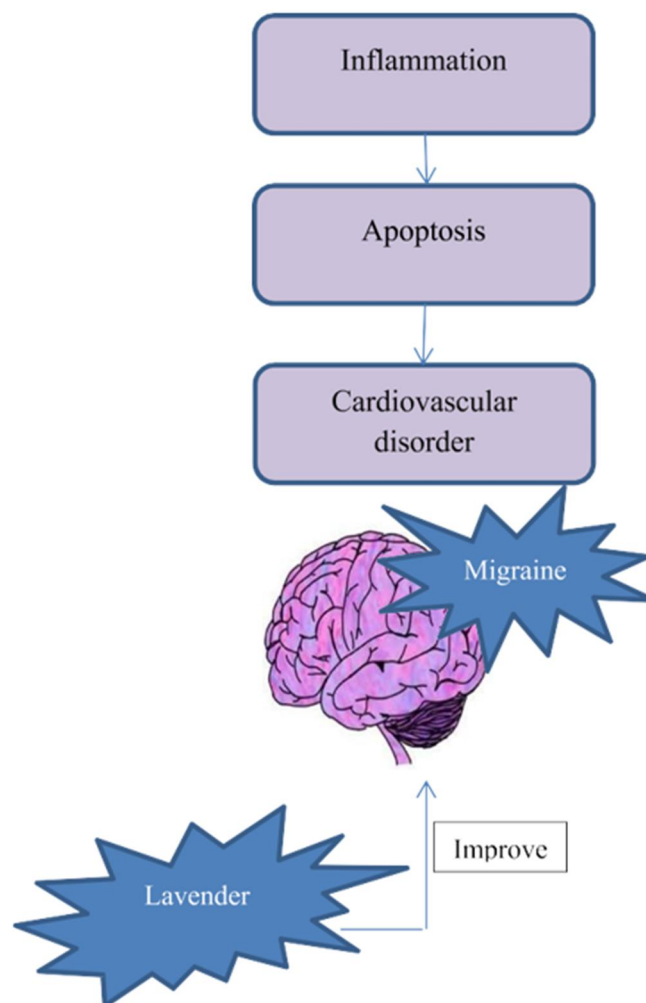


Fig. 7 Linalyl acetate (LA) in lavender oil exerts anti-migraine effects due to its anti-inflammatory effect. Also, isolated aortic vasodilation is caused by LA.



II. CONCLUSION

Lavender is an important medicinal plant. Belonging to the family lamiaceae, this is an important medicinal plant in traditional medicine. It is used in various neurological disorders, including Alzheimer's, depression, epilepsy, anxiety, and migraine.

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