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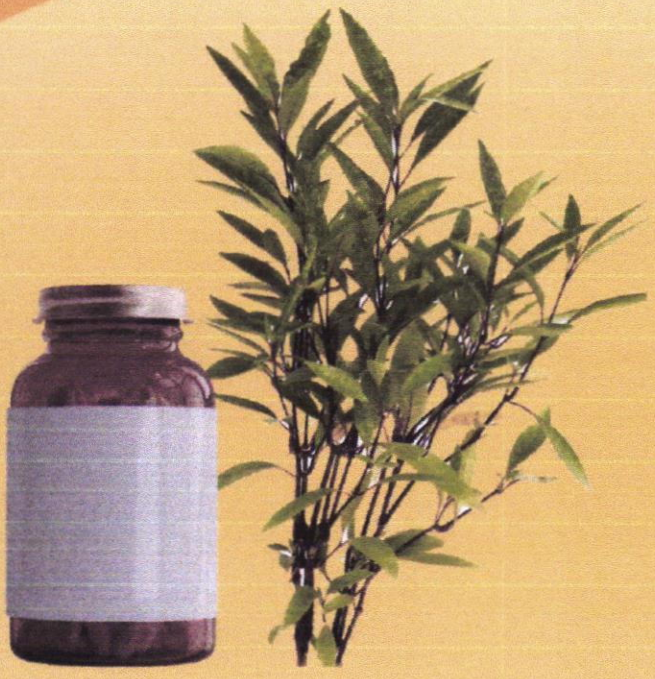

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Molecular Docking of Active Compound of *Lavandula angustifolia* Mill Essential Oil against N-methyl-D-aspartate (NMDA) Receptor

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Abstract

***Background**: Lavender oil is widely known to possess a relaxant effect to relieve stress, anxiety, and depression. Linalyl acetate, linalool, geranyl acetate, and β-caryophyllene were the major constituents of lavender oil that potentially act on NMDAR (N-methyl-d-aspartate receptors), and emerging targets in the treatment of depression.* ***Objective**: This study aims to predict the binding of lavender compounds to NMDA receptors using an in silico model.* ***Methods**: The ligands of the docking study were four major chemical compounds of lavender oil, i.e., linalyl acetate, linalool, geranyl acetate, and β-caryophyllene. 5YE was defined as a native ligand, while memantine, an NMDAR antagonist, was used as a reference ligand. The NMDAR structure was taken from Protein Data Bank (1D 5H8Q), while the lavender compound was sketched in Chem3D. Autodock 4.2 was used to perform the docking analysis.* ***Results**: The result showed that beta-caryophyllene had the most potent interaction with NMDAR (free binding energy was -8.02 kcal/mol and inhibitory constant was 1.32 μM).* ***Conclusion**: The docking results suggest that beta-caryophyllene could be an NMDAR antagonist and be developed as a treatment for depression.*

***Keywords**: depression, lavender oil, molecular docking, NMDAR*

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INTRODUCTION

Essential oil from black seed (*Nigella sativa*), Japanese rush (*Acorus gramineus*), lavender (*Lavandula angustifolia*), blue gum (*Eucalyptus globulus*), peppermint (*Mentha piperita*), rosemary (*Rosmarinus officinalis*), sambac jasmine (*Jasminum sambac*), black pepper (*Piper nigrum*) and several other plants have been reported to have neuroprotective effects (Ayaz *et al.*, 2017). Lavender (*Lavandula angustifolia*) is the most widely used essential oil for aromatherapy (Wells *et al.*, 2018). Lavender oil is known for its delicate aroma and is commonly used in the perfume, flavoring, and cosmetic industries. Lavender has a long history of medicinal use and is reported to have antidepressants, anti-anxiolytic, sedative, analgesics, and calming effects (Wells *et al.*, 2018; Kang *et al.*, 2019; Lizarraga-Valderrama, 2021). Aromatherapy is considered therapeutically effective because of the inhaled volatile compounds' psychological effects, which are believed to act through the limbic system, particularly the amygdala and hippocampus (Fung *et al.*, 2021). While the exact cellular mechanism of action is unknown, it is predicted that lavender (based on studies on *L. angustifolia*) may have an effort similar to benzodiazepines and may enhance the effects gamma-aminobutyric acid (Lizarraga-Valderrama, 2021). In their publication, López *et al.* (2017) reported that the main constituents of lavender essential oil analyzed by GC-MS were linalyl acetate (52.1%), linalool (37.4%), geranyl acetate (5.4%), and β-caryophyllene.

Stress is one of the most common psychological disorders and is generally the beginning of other psychiatric disorders, such as anxiety, insomnia, and depression (López *et al.*, 2017). Currently, drugs for depression exert their effects by increasing the levels of biogenic amines, i.e., norepinephrine (NE), dopamine (DA), and serotonin (5HT) by various mechanisms, such as inhibiting the degradation or reuptake of neurotransmitters. However, these drugs have serious side effects, including sexual dysfunction, weight gain, sleep disturbance, etc., leading to an effective and better-tolerated antidepressant. On the other hand, the NMDA receptor family (N-methyl-D-aspartate) has received particular attention in psychiatric disorders, especially major depressive disorder (Pochwat *et al.*, 2019). Therefore, direct targeting of the NMDA receptor may yield alternative strategies for treating depression.

Docking is the process of interaction between two molecules in three-dimensional space. Molecular docking is a valuable tool in structural molecular biology and is a potential field for new drug discovery. This method is widely used to predict the binding mode of the ligand to the protein. Applications of docking techniques include the prediction of new drug binding modes and the screening of active compounds. This study aims to predict the binding of lavender compounds to the receptors using an in silico model.

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MATERIALS AND METHODS

Protein preparation

The crystal structure of the NMDA with ID 5H8Q was downloaded in PDB file format from the RCSB protein data bank and imported into AutoDock 4.2. Polar hydrogens and Kollman charges are then added to the protein. Considering that the water molecule is not involved in the ligand-receptor bonding process, the water molecule is removed. This step of removing water molecules may also significantly improve computations and prevent distortions that might occur.

Ligand preparation

The molecular structures of four major compounds from lavender oil are given in Figure 1. The structures of linalyl acetate, linalool, geranyl acetate, and β-caryophyllene were drawn using Chem3D. Next, energy minimization of each ligand was carried out using the MM4 force field, and then the ligands were stored in mol2 format. Finally, the ligands are imported into the AutoDock workspace. The nonpolar hydrogens were merged for each ligand, and the gasteiger charges were computed.

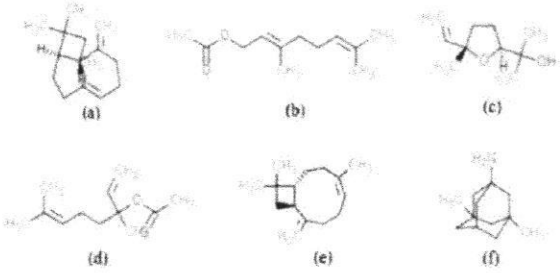

Figure 1. The molecular structure of (a) beta-caryophyllene, (b) geranyl acetate, (c) linalool, (d) linalyl acetate, (e) 5_YE, and (f) memantine

Docking

Molecular docking was performed using Autodock 4.2. Before the docking study was performed, the docking parameters and algorithm were validated by re-docking the native ligand to the target receptor. According to the native ligand, a grid box of 14.595 Å x -14.301 Å x -25.15Å along x, y, and z was defined as a binding site. The docking parameters were left as

default, except the docking run was set to 30 for each compound. Finally, the Lamarckian Genetic Algorithm generated a molecular docking study. Root mean standard deviation (RMSD) lower than 2 Å suggested that the method could consistently predict the natural conformation of the ligand-receptor. Favorable conformation was selected based on the lowest energy binding and inhibitory constant (*Ki*).

Statistical analysis

The quantitative relationship between the chemical structure in lavender oil and its biological activity was determined by correlation analysis in the SPSS program. Analysis of the structure-activity relationship was carried out using the LFER Hansch model. In this study, lipophilic parameters involved were partition coefficient (logP), electronic parameter, i.e., ligand-receptor bond energy (binding energy), and steric parameter, i.e., molar refraction (MR). Linear and nonlinear regression analysis was performed between lipophilic, steric, and electronic parameters with antidepressant activity. The equation with the best relationship significance was selected based on the values of r, F, and SD.

RESULTS AND DISCUSSION

The docking protocol was validated through a re-docking experiment using the native ligand. A root means square deviation (RMSD) value of less than 2 Å was observed, suggesting that the ligand-receptor conformation has a high docking accuracy. Another method to validate the docking parameters and algorithm is docking decoy ligands to the receptor's binding site (Huang *et al.*, 2006). Decoys are compounds that share similar physical properties with the reference ligand but may not bind to the target.

Table 1. Results of molecular docking of *Lavandula angustifolia* Mill compound with NMDA1/2 (5H8Q) receptors

No	Ligand	Binding Energy (kcal/mol)	Estimated Binding Constant (Ki) (μM)	Hydrogen bond	Interacting Amino Acid	Number of Binding Site Similar to Native Ligand
1	Beta-caryophyllene	-8.02	1.32	-	THR A: 242, GLU A: 132, PHE A: 130, VAL A: 131, GLY B: 250, PRO B: 141, PRO A: 129, TYR B: 144, ILE B: 128	9
2	Geranyl acetate	-6.49	17.60	-	PHE A: 130, VAL A: 131, GLU A: 132, PRO A: 129, TYR B: 144, THR A: 241, THR A: 242, PRO B: 141, GLY A: 243, HIS B: 273, LEU B: 270, LYS B: 140	12
3	Linalool	-5.91	46.83	THR A: 242	ILE B: 269, GLU A: 132, TYR B: 144, LYS B: 143, LEU B: 270, THR A: 241, LYS B: 140, HIS B: 273, THR A: 242, PRO A: 129, GLY A: 243, ILE A: 116, PRO B: 141	13
4	Linalyl acetate	-6.37	21.33	-	GLU A: 131, PHE A: 130, VAL A: 131, PRO A: 129, GLY A: 243, LYS B: 140, THR A: 242, LYS B: 143, PHE B: 142, THR A: 241, HIS B: 275, THR B: 144,	9
5	5YE (native ligand)	-10.43	22.75	THR A: 242	PHE B: 142, LYS B: 143, THR A: 241, THR A: 242, HIS B: 273, LYS B: 140, ILE A: 116, LEU B: 270, GLY A: 243, PRO B: 141, PHE A: 130, VAL A: 131, VAL A: 266, TYR B: 144, PRO A: 129, GLU A: 132, GLY B: 250	All
6	Memantine	-8.72	407.81	THR A: 133, THR A: 242, GLU A: 132	THR A: 133, THR A: 242, THR A: 241, GLU A: 132, PRO A: 129, HIS B: 273, TYR B: 144, PRO B: 141, GLY A: 243	9

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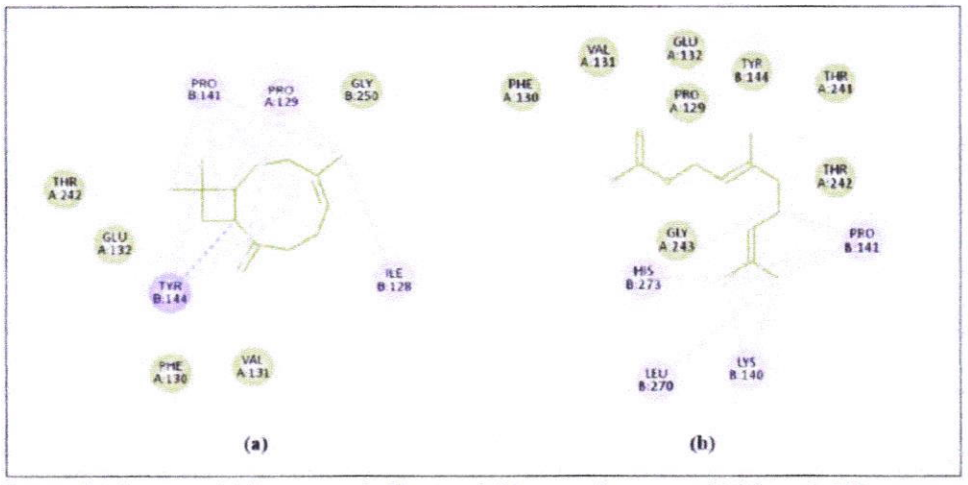

Figure 2. Interaction between (a) beta-cayophyllene and (b) geranyl acetate with N-methyl D-aspartate (NMDA) receptors

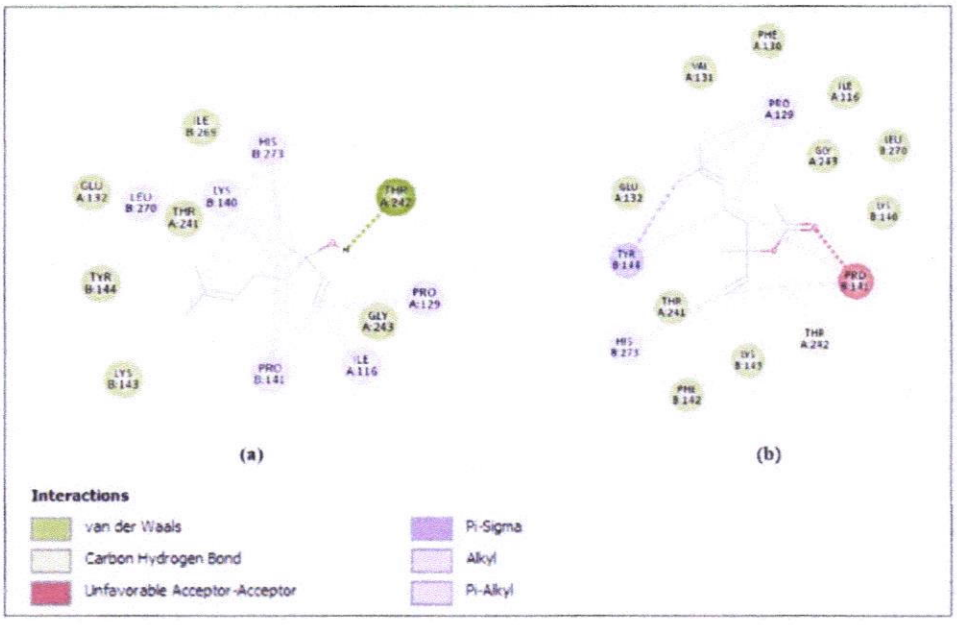

Figure 3. Interaction between (a) linalool and (b) linalyl acetate with N-methyl D-aspartate (NMDA) receptors

The molecular docking of the Lavandula angustifolia Mill compound components against the NMDA1/2 (5H8Q) receptor obtained using Autodock are presented in Table 1, while the 2D interactions are visualized in Figure 2 and 3. The docking results showed that all ligands from lavender oil were docked on the same binding site as the native ligand. Similar interactions with binding site residue indicate that the compound might exhibit inhibitory activity toward the receptor. Based on the docking data, we found that beta-caryophyllene has the lowest energy required to bind to the targeted receptor compared to other compounds. The binding energy is -8.02 kcal/mol, and Ki is 1.32 µM.

Furthermore, the low binding energy value indicated the stability of the ligand-receptor interaction. Interestingly, beta-caryophyllene has no hydrogen bond with the target receptor. The interaction formed is mainly hydrophobic via Pro B: 141, Pro A: 129, Tyr B: 144, and Ile B: 128 residues. Meanwhile, 5YE (native ligand) had binding energy of -10.43 kcal/mol and made one hydrogen bond, one pi-pi stacked, and five hydrophobic interactions (Figure 4a). Memantine, an NMDAR antagonist, had binding energy of -8.72 kcal/mol and formed three hydrogen bonds, one carbon-hydrogen bond, and four hydrophobic interactions (Figure 4b). Therefore, by comparing the binding energy of the three complexes, it is suggested that the contribution of hydrophobic interaction to binding affinity is comparable to electrostatic interaction.

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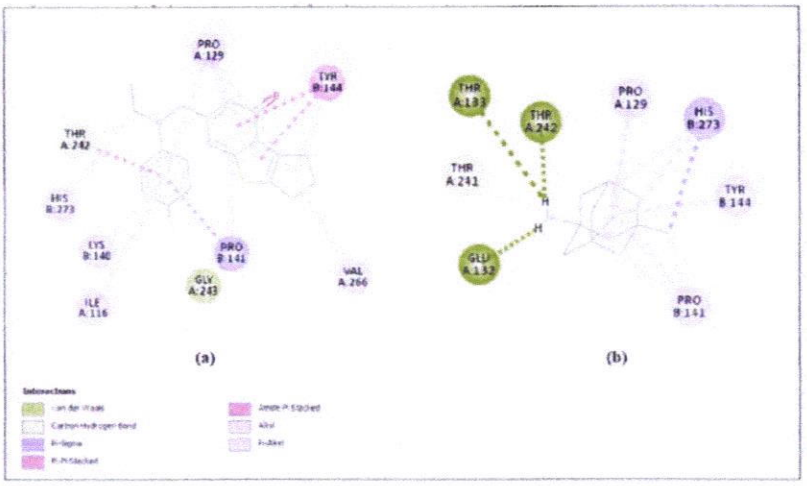

Figure 4. Interaction between (a) 5YE (native ligand) and (b) memantine (reference ligand) with N-methyl D-aspartate (NMDA) receptors

Table 2. The value of electronic properties (σ), lipophilic properties (π), steric properties (RM), and log activity of each lavender compound

Ligand	σ	π	π^2	RM	Log A
Beta-caryophyllene	-8.02	4.32	18.662	67.452	-0.12
Geranyl acetate	-6.49	3.25	10.563	60.334	-1.245
Linalool	-5.91	2.55	6.503	50.206	-1.67
Linalyl acetate	-6.37	3.189	10.170	59.357	-1.33

Linalool is the only compound that forms a hydrogen bond with the targeted receptor, but this compound has the highest energy to bind to the receptor (-5.91 kcal/mol) and the highest *Ki* (46.83 µM). Meanwhile, the ester of linalool, linalyl acetate, has a slightly higher binding affinity, evidenced by the free binding energy of -6.37 kcal/mol and *Ki* of 21.33 µM. The in-vitro study supports this result reporting the monoterpenes (linalool and linalyl acetate) can inhibit NMDA receptor, in which linalyl acetate has the greater inhibition against the receptor (0.54 mM and 2.3 mM for linalyl acetate and linalool, respectively) (López *et al.*, 2017). Indeed, the presence of the acetate group is predicted to increase the compound's acts on the NMDA receptor. This may explain the higher affinity of geranyl acetate geranyl acetate's affinity toward the receptor (binding energy -6.49 kcal/mol and *Ki* 17.60), compared to linalool. To summarize the findings, the lavender compound with the best affinity against NMDA receptors is beta-caryophyllene, followed by geranyl acetate, linayl acetate, and linalool.

The value of electronic, lipophilic, and steric properties of each lavender compound is given in Table 2. Statistical analysis was conducted to examine the correlation between the compound structure and its activity. It was found that the electronic property (binding energy) is the parameter that is most related to compound activity, as indicated by the values of r, r^2, F, and S. The closer to 1 the value of r, the higher the value of r^2 and F, and the smaller the value of S, the greater the significance of the relationship between physical chemistry parameters and compound activity. The linear regression equation of electronic parameters with antidepressant activity is Log A = 0.992 σ + 2.229 (r = 0.992; r^2 = 0.984; F = 124.658; S = 0.2; Sig 0.008), while the linear equation of lipophilic parameters is Log A = 0.418 π - 10.457 (r = 0.418; r^2 = 0.175; F = 0.424; S = 16.067; Sig = 0.582), and the equation of steric parameters is Log A = 0.411 RM - 1.065 (r = 0.411; r^2 = 0.169; F = 0.406; S = 1.672; Sig = 0.589). These results indicate that the binding energy value is the most significant parameter in influencing the antidepressant activity of compounds in lavender.

A recent systematic review and meta-analysis of randomized controlled studies reported that lavender oil significantly reduced depressive scores compared to the control group (Firoozeei *et al.*, 2021). As lavender oil is mainly used in the inhalation method, it can cross the blood-brain barrier, has a faster onset, and limited side effects. Inhaled essential oil is thought to have better bioavailability than oral drugs, ascribed to its high lipid solubility and minimal to zero hepatic metabolisms (Ayaz *et al.*, 2015). The molecular pathway of lavender oil in exerting its antidepressant and antianxiety effect is

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reported through the inhibition of NMDA receptor, $5HT_{1A}$ receptor, serotonin transporter, voltage-gated calcium channel, and neurotoxic agent as hydrogen peroxide (López *et al.*, 2017; Firoozeei *et al.*, 2021). Linalool is the most studied lavender oil compound for its anxiolytic effect. Linalool was reported to have a relaxant effect, increased social interaction and reduced aggressive behavior in the animal model (Ayaz *et al.*, 2017). Previously, it was reported that beta-caryophylline could improve rat depressive-like behavior and suppress the altered hippocampal expression of BNDF, COX-2, and CB2 receptors (Hwang *et al.*, 2020).

Targeting the classic monoaminergic receptor, the current antidepressants on the market, such as selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI), have become unfavorable to the lack of efficacy and prominent side effects. This limitation leads to finding an alternative antidepressant with better efficacy and tolerability. In recent years, the glutamate receptor has been emerging as a key target of antidepressants, owing to the rapid and robust antidepressant effect of ketamine, an NMDA receptor antagonist (Machado-Viera *et al.*, 2017). Glutamate is the main excitatory neurotransmitter in the brain and is involved in neurotoxicity by activating the NMDA receptor. Thus, targeting the NMDA receptor may exert a neuroprotective effect that improves depressive symptoms. In this study, we find that the primary compound of lavender oil has an affinity to bind to the NMDA receptor and act as an inhibitor. Beta-caryophyllene has the best binding affinity, making it a promising compound for further development as an NMDA receptor antagonist and a new candidate of antidepressant.

Beta-caryophyllene is a component of *L. angustifolia* with a molecular weight of 204.357 g/mol and a logP of 4.73. Geranyl acetate has high absorption in the gastrointestinal tract, where it is predicted that 94.85% will be absorbed through the intestine. This compound also has good permeability to the blood-brain barrier, with a predictive value of 0.733 logBB. In addition, geranyl acetate is not a substrate for P-gp, a transporter that acts as a biological barrier that removes toxins and xenobiotics from cells (Pires *et al.*, 2015).

Despite its wide application, molecular docking also has a limitation, including the wrong binding site to the target, the choice of docking pose, the uncertainty of whether a compound is a true antagonist or agonist, and the nonlinearity of the docking and molecular dynamic simulation results (Chen, 2014). The molecular dynamic simulation is warranted to further investigate the stability of ligand binding poses to protein (Liu *et al.*, 2017).

CONCLUSION

In silico molecular docking, the analysis revealed that beta-caryophyllene has the lowest binding energy (-8.02 kcal/mol) to NMDA receptor, suggesting its potential as an inhibitor of the NMDA receptor its future use as an antidepressant agent. Analysis of the structure-activity relationship indicates that the ligand-receptor bond energy was the parameter that most influenced the compound's activity. Further preclinical research of the compound in lavender oil needs to be carried out to validate the in silico results.

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AUTHOR CONTRIBUTIONS

Conceptualization, B.R.W.L., A.S.B., J.K.; Methodology, B.R.W.L., A.S.B., C.A.; Software, B.R.W.L.; Validation, C.A.; Formal Analysis, B.R.W.L.; Investigation, B.R.W.L.; Resources, J.K.; Data Curation, B.R.W.L., C.A., J.K.; Writing - Original Draft, B.R.W.L.; Writing - Review & Editing, J.K.; Visualization, B.R.W.L.; Supervision, C.A.; Project Administration, B.R.W.L.; Funding Acquisition, J.K.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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