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POTENTIAL OF FARNESOL AS A MAO-A INHIBITOR CANDIDATE FOR THERAPY OF MENTAL HEALTH DISORDERS: AN IN SILICO STUDY

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Abstract

Mental health disorders, particularly depression, remain a global problem with a high prevalence among university students. Conventional therapy using chemical antidepressants is often limited by side effects, delayed onset of action, and limited effectiveness. Farnesol, a sesquiterpene found in essential oils, has been reported to exhibit biological activity in the central nervous system. This study aims to explore the potential of farnesol as a candidate Monoamine Oxidase-A (MAO-A) inhibitor through an in silico approach. Docking studies were performed on 5HT1A, 5HT2A, GABA, and MAO-A receptors using SwissDock, with the ligand prepared from the PubChem database. Binding interactions were visualized using ChimeraX and LigPlot, while toxicity evaluation was analyzed using SwissADME and ADMETlab 2.0. The results showed that farnesol had the best binding energy toward the MAO-A receptor (-8.43 kcal/mol) compared with the control compound phenelzine (-6.62 kcal/mol). Farnesol also showed good blood-brain barrier penetration ability and a low toxicity profile. Therefore, farnesol has the potential to be developed as a natural antidepressant candidate derived from essential oils. Further in vitro and in vivo studies are required to verify these findings.

Keywords: Farnesol, MAO-A, antidepressant, in silico, essential oil

INTRODUCTION

Mental health disorders are a global issue that significantly impacts young people, including college students. According to the World Health Organization (2020), more than 350 million people worldwide experience mental disorders, with depression projected to be the leading cause of global disease burden by 2030 (Malhi & Mann, 2018). Symptoms of depression include mood swings, loss of motivation, impaired concentration, and the risk of suicidal behavior, which drastically reduce an individual's quality of life (Rakel, 1999; Ribeiro et al., 2018; Shim et al., 2019).

In Indonesia, the prevalence of mental health disorders is also increasing. The 2018 Basic Health Research data reported that approximately 470,000 individuals suffer from schizophrenia, while mental-emotional disorders such as depression and anxiety affect more than 19 million people (Ministry of Health of the Republic of Indonesia, 2018; Puspitasari et al., 2020). This situation emphasizes the importance of more effective prevention strategies and alternative therapies to support the mental well-being of students.

Conventional pharmacological therapy using synthetic antidepressants has proven effective, but has limitations, such as slow onset of action, a limited spectrum of activity, and frequent side effects. Only around 30–40% of patients achieve full remission, while others remain at risk of relapse despite treatment (Davidson, 2010; Katona & Katona, 2014). Therefore, developing therapies based on natural compounds is a promising approach.

Essential oils are known to contain active compounds with various pharmacological activities, including anti-inflammatory, anticonvulsant, and effects on the central nervous system (Guimarães et al., 2013; Bakour et al., 2018; Masoumi-Ardakani et al., 2016). Farnesol, a sesquiterpene found in essential oils, can penetrate the blood-brain barrier and potentially inhibit the enzyme Monoamine Oxidase-A (MAO-A), an enzyme involved in the degradation of serotonin, dopamine, and norepinephrine (Uzzaman et al., 2021; Yanez et al., 2012). Inhibiting MAO-A can increase the availability of these neurotransmitters, thereby helping to improve symptoms of depression. Based on this background, this study aims to explore the potential of farnesol as a candidate MAO-A inhibitor through an in silico approach.

RESEARCH METHODS

This study is an in silico study with a molecular docking- based computational approach to evaluate the potential of farnesol as a candidate Monoamine inhibitor. Oxidase-A (MAO-A). All stages of the study were conducted in silico using web-based software and computer applications at the Military Pharmacy Laboratory, Faculty of Military Pharmacy, Republic of Indonesia Defense University during July–August 2025. The target receptors used were 5HT1A, 5HT2A, GABA, and MAO-A, obtained from the Protein Data Bank (PDB). Protein quality validation was performed using Errat , Verify 3D , and Procheck via the SAVES server (UCLA). Farnesol was obtained from the PubChem database . Ligand and receptor structure preparation was performed with UCSF ChimeraX , including the removal of water molecules, the addition of hydrogen atoms, and the separation of the receptor chain. Ligand-receptor docking was performed using SwissDock . Affinity analysis was determined based on the lowest binding energy value. The antidepressants phenelzine, diazepam, buspirone, vilazodone, risperidone, and olanzapine were used as controls. Ligand binding to receptor amino acid residues was visualized using UCSF. ChimeraX and LigPlot . Pharmacokinetic and toxicity predictions were performed using SwissADME and ADMETlab. 2.0 to assess the safety of drug candidates, including blood-brain barrier penetration ability.

DISCUSSION

Farnesol Affinity for Target Receptors

Molecular docking results using SwissDock showed that in three receptors, namely 5HT1A, 5HT2A, and GABA, none of the 42 essential oil compounds had lower binding energy than the control drug. However, in the MAO-A receptor, farnesol showed better binding energy (-8.43 kcal/mol) compared to phenelzine as a control drug (-6.62 kcal/mol). This difference indicates that farnesol has a higher binding affinity, so it has the potential as a candidate to replace phenelzine based on in silico studies .

This study aims to evaluate the potential of farnesol as a candidate MAO-A inhibitor using an in silico approach . Docking results showed that of the 42 essential oil compounds analyzed, farnesol had the lowest binding energy to the MAO-A receptor (-8.43 kcal/mol), better than phenelzine as a control drug (-6.62 kcal/mol). This difference indicates that farnesol has the potential to have a higher affinity for the active pocket of MAO-A. This finding is in line with previous studies that stated that MAO-A inhibition can increase the availability of serotonin, dopamine, and norepinephrine in synapses, making it effective in treating symptoms of depression (Yanez et al., 2012; Katona & Katona, 2014).

Comparison of Farnesol with Control Drugs and Other Essential Oil Compounds

Based on the molecular docking results presented in Table 1, farnesol demonstrated the ability to bind to all target receptors analyzed, namely 5HT1A, 5HT2A, GABA, and MAO-A. The binding energy values of farnesol to each receptor were −7.89 kcal/mol, −7.64 kcal/mol, −7.11 kcal/mol, and −8.43 kcal/mol, respectively. The more negative the binding energy value indicates the stronger affinity of the ligand for the target receptor. Of all the receptors tested, the highest affinity of farnesol was obtained for the MAO-A receptor with a binding energy value of −8.43 kcal/mol. This value is even lower than the control phenelzine as an MAO-A inhibitor, which is −6.62 kcal/mol. These results indicate that farnesol has the potential to have stronger inhibitory activity against MAO-A than the control ligand.

At other receptors, the binding energy of farnesol is still higher than that of the control drugs specific to each receptor. At the 5HT1A receptor, the binding energy value of farnesol (−7.89 kcal/mol) is higher than that of vilazodone (−8.88 kcal/mol) and risperidone (−9.04 kcal/mol). At the 5HT2A receptor, the affinity of farnesol (−7.64 kcal/mol) is also still lower than that of buspirone (−8.82 kcal/mol) and risperidone (−8.89 kcal/mol), although slightly better than olanzapine (−7.84 kcal/mol). Meanwhile, at the GABA receptor, the binding energy of farnesol (−7.11 kcal/mol) is still slightly higher than that of diazepam as a control (−7.30 kcal/mol). These results indicate that farnesol activity tends to be more selective towards MAO-A receptors than towards other neurotransmitter receptors.

The selectivity of farnesol towards MAO-A is further strengthened by the results of comparisons with other essential oil compounds presented in Table 2. Farnesol has the lowest binding energy value on all receptors compared to the 41 other essential oil compounds analyzed. At the MAO-A receptor, the compound with the closest affinity to farnesol is nerolidol with a binding energy of −8.02 kcal/mol, while other compounds show lower affinities, such as 2,4,5-trimethoxycinnamic acid (−7.51 kcal/mol) and octylacetate (−7.42 kcal/mol). A similar pattern is also seen at the 5HT1A, 5HT2A, and GABA receptors, where farnesol still shows the lowest binding energy compared to other essential oil compounds. These results confirm that farnesol is the main compound with the most potential in interacting with protein targets related to antidepressant activity.

Table 1. Comparison of binding energies of farnesol with control drugs at various target receptors.

No	Ligand	Receptor			
		5HT1A	5HT2A	GABA	MAO-A
1	Farnesol	-7.89	-7.64	-7.11	-8.43
2	Phenelzine (Control)	-	-	-	-6.62
3	Diazepam (Control)	-	-	-7.30	-
4	Buspirone (Control)	-	-8.82	-	-
5	Viladozone (Control)	-8.88	-	-	-
6	Risperidone (Control)	-9.04	-8.89	-	-
7	Olanzapine (Control)	-	-7.84	-	-

Table 2. The binding energy value of essential oil compounds with the best affinity for target receptors.

No	Ligand	Receptor			
		5HT1A	5HT2A	GABA	MAO-A
1	Farnesol	-7.89	-7.64	-7.11	-8.43
2	Dehydrofukinone	-6.92	-7.20	-6.92	-7.07
3	Aromadendrene	-7.10	-7.26	-	-7.03
4	Sphatulenol	-6.96	-7.20	-6.78	-7.02
5	Citronello	-7.03	-6.66	-6.38	-7.05
6	Elemicin	-6.84	-7.26	-6.77	-7.11
7	Nerolidol	-7.55	-7.40	-6.86	-8.02
8	Verticiol	-7.36	-7.27	-6.62	-7.34
9	2,4,5-Trimethoxycinnamic Acid	-7.10	-7.76	-7.02	-7.51
10	Octylacetate	-7.00	-6.90	-6.86	-7.42
11	Citronellylpropionate	-7.18	-6.96	-7.06	-7.34

Biologically, farnesol's high affinity for MAO-A indicates a potential mechanism of action through inhibition of the degradation of monoamine neurotransmitters, such as serotonin, dopamine, and norepinephrine. MAO-A inhibition can increase the availability of these neurotransmitters at the synapse, thus contributing to the antidepressant effect. Furthermore, selectivity toward MAO-A is also important because it can reduce non-specific interactions with other receptors that have the potential to cause side effects, as is often found in older generation antidepressants. Thus, the docking results indicate that farnesol has good prospects as a candidate for an essential oil-based antidepressant compound, especially through the mechanism of MAO-A inhibition (Malhi & Mann, 2018).

Interaction of Farnesol with MAO-A

Docking visualization using UCSF ChimeraX showed that farnesol stably occupies the active pocket of the MAO-A enzyme. This compound binds to the same active site as the control ligand, supporting the predicted inhibitor activity. Further analysis using LigPlot+ revealed the binding pattern of farnesol to amino acid residues within the active pocket of MAO-A. This interaction diagram confirmed the presence of hydrophobic and non-covalent bonds that contribute to complex stability. Visualization of ligand–receptor interactions using UCSF ChimeraX and LigPlot+ supported the docking data, demonstrating the presence of non-covalent and hydrophobic bonds that contribute to the stability of the farnesol–MAO-A complex. This binding mechanism may explain the high affinity potency of farnesol, consistent with literature reporting that monoterpene and sesquiterpene compounds have neuroprotective activity through modulation of the monoamine system (Guimarães et al., 2013).

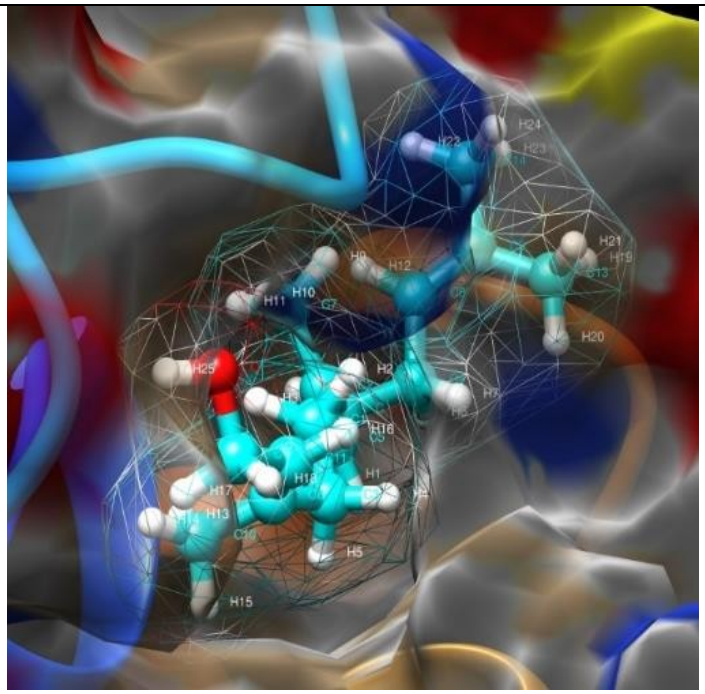

Figure 1. 3D visualization of the docking results of farnesol with the MAO-A receptor (UCSF ChimeraX).

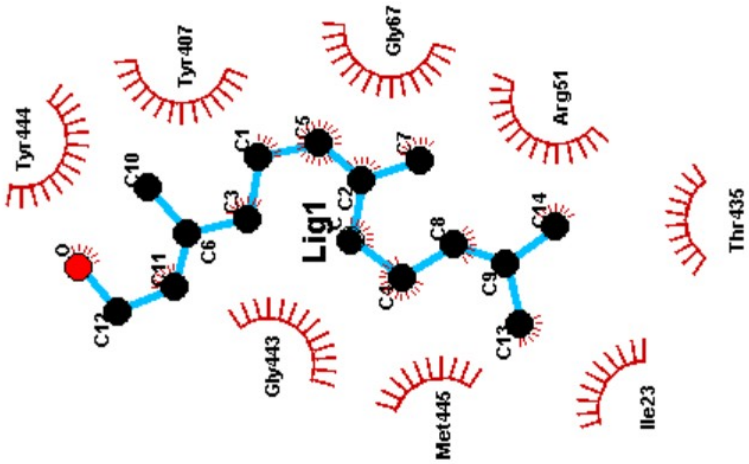

Figure 2. Interaction diagram of farnesol with MAO-A using LigPlot+

Prediction of Pharmacokinetics, BBB Penetration, and Toxicity

Pharmacokinetic evaluation of farnesol using SwissADME demonstrated lipophilic properties that support membrane absorption. Boiled-egg analysis results indicated that farnesol is predicted to penetrate the blood-brain barrier (BBB), potentially reaching the central nervous system.

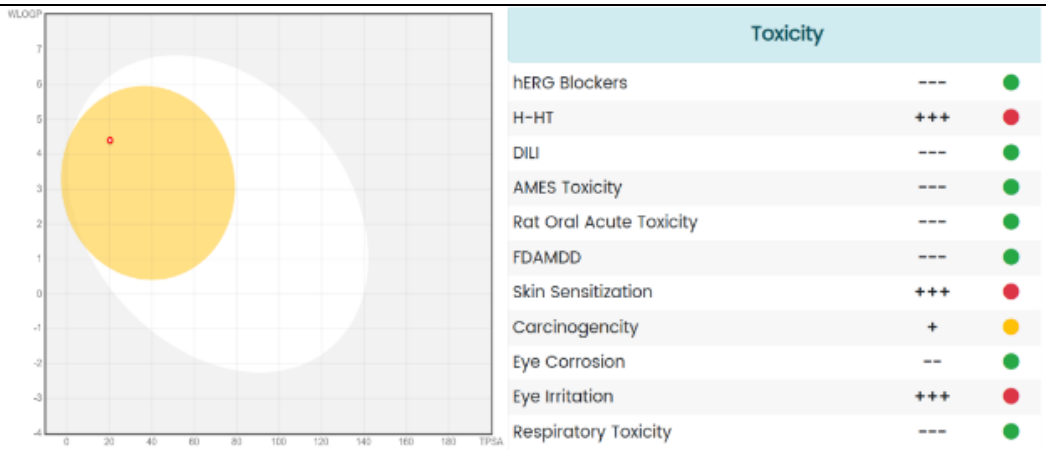

Figure 3. Prediction of farnesol penetration through the blood-brain barrier using the boiled-egg model (SwissADME).

Furthermore, prediction results using ADMETlab 2.0 indicate that farnesol has a good safety profile, with a low risk of hepatotoxicity and mutagenicity. Pharmacokinetic prediction of farnesol using SwissADME indicates its ability to penetrate the blood-brain barrier , which is an important requirement for compounds with antidepressant activity. Further analysis using ADMETlab 2.0 also shows a relatively safe toxicity profile, with a low risk of hepatotoxicity and mutagenicity. These results strengthen the potential of farnesol to be developed as a candidate for natural compound-based antidepressant therapy.

Potential Mechanism of Farnesol as an MAO-A Inhibitor

Based on docking results and pharmacokinetic analysis, farnesol is predicted to inhibit MAO-A activity. This inhibition has the potential to increase the availability of monoamine neurotransmitters, including serotonin, dopamine, and norepinephrine, which play a key role in mood regulation.

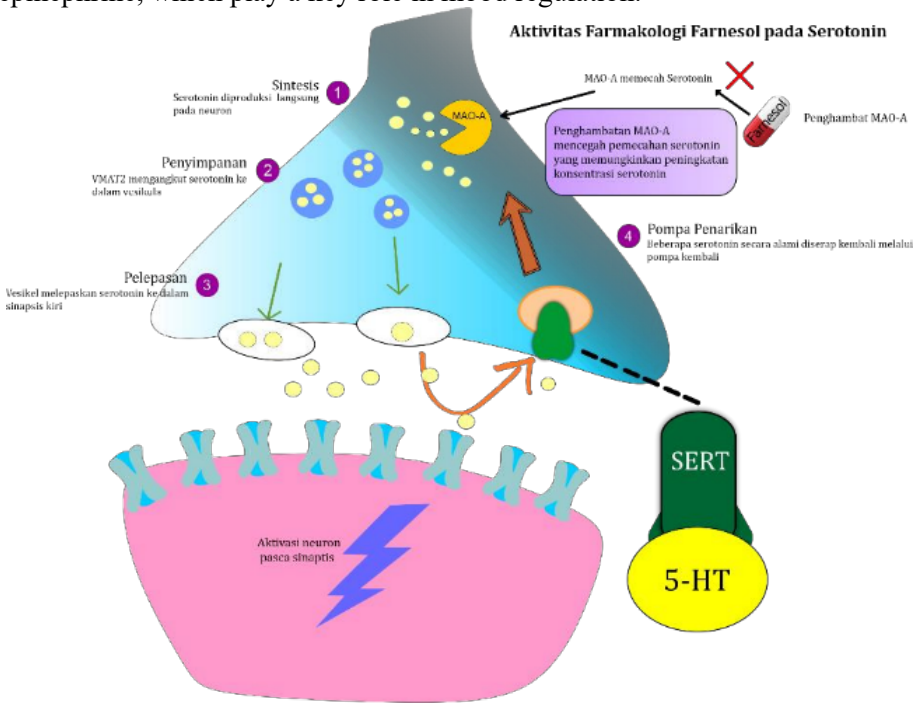

Figure 4. Mechanism of Farnesol as an MAO-A Inhibitor

Implications, Limitations, and Directions for Further Research

However, this study has limitations due to its in silico approach . Further validation through in vitro and in vivo studies is needed to confirm farnesol's biological efficacy, including systemic toxicity testing and pharmacodynamic evaluation. Further research is also needed to explore bioavailability, effective dosage, and potential drug interactions if farnesol is developed as a clinical therapy.

Further research is needed to validate farnesol's potential through in vitro and in vivo approaches , particularly regarding its pharmacological activity as an MAO-A inhibitor, its systemic toxicity profile, and its bioavailability. Clinical trials are also recommended as a next step to confirm the effectiveness and safety of farnesol before it can be developed as a natural compound-based antidepressant therapy.

CONCLUSION

in silico study suggests that farnesol, a sesquiterpene found in essential oils, has the potential to be a new drug candidate for mental health disorders. This compound has a high affinity for the MAO-A receptor and plays a role in increasing serotonin levels. Furthermore, its predicted low toxicity supports its safety profile as a drug candidate.

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