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Innovation of Areca catechu Compounds Combined with Fluoxetine as Antidepressant by In Silico Method

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Abstract
Depression is a mental illness that has become a common problem worldwide with more than 300 million cases. The study aimed to determine the effectiveness of natural compound modification with synthetic compounds as new antidepressant drug candidates. The method used in the research is In Silico approach using ChemSketch software, BIOVIA Discovery Studio Visualizer (DSV), and Autodock Vina. The bond-free energy result from a combination of arecoline, homoarecoline and guvacoline with fluoxetine on 2Z5Y protein were -7.1 kcal/mol; -7.1 kcal/mol and -7.6 kcal/mol, respectively. Meanwhile, in 2NW8 protein, the bond free energy observed were -6.3 kcal/mol; -6.3 kcal/mol, and -8.8 kcal/mol, respectively. Based on bond-free energy data, the additive interaction of arecoline-fluoxetine and fluoxetine-homoarecoline on MAO-A protein (2Z5Y) was barely different from fluoxetine itself. Meanwhile, the additive interaction of guvacoline-fluoxetine was better with serotonin precursor protein (2NW8) rather than MAO-A protein (2Z5Y).
***Keywords**: Antidepressants, arecoline, fluoxetine, guvacoline, homoarecoline*

Abstrak
Depresi merupakan penyakit mental yang telah menjadi masalah umum di seluruh dunia dengan lebih dari 300 juta kasus. Penelitian ini bertujuan untuk mengetahui efektivitas modifikasi senyawa alami dengan senyawa sintetik sebagai kandidat obat antidepresan baru. Metode yang digunakan dalam penelitian adalah pendekatan secara In Silico dengan menggunakan software ChemSketch, BIOVIA Discovery Studio Visualizer (DSV), dan Autodock Vina. Energi bebas ikatan yang dihasilkan dari kombinasi arekolin, homoarekolin dan guvakolin dengan fluoksetin pada protein 2Z5Y adalah -7,1 kkal/mol; -7,1 kkal/mol dan -7,6 kkal/mol. Sedangkan pada protein 2NW8, energi bebas ikatan yang teramati adalah -6,3 kkal/mol; -6,3 kkal/mol, dan -8,8 kkal/mol. Berdasarkan data energi bebas ikatan, interaksi aditif arekolin-fluoksetin dan homoarekolin-fluoksetin pada protein MAO-A (2Z5Y) hampir tidak berbeda dengan fluoksetin itu sendiri. Sementara itu, interaksi aditif guvakolin-fluoksetin lebih baik dengan protein prekursor serotonin (2NW8) daripada protein MAO-A (2Z5Y).
***Kata kunci**: Antidepresan, arekolin, fluoksetin, guvakolin, homoarekolin*

1. Introduction

Depression is a mental disorder marked by unstable emotions, difficulty concentrating, a lack of interest in exciting things, physical disturbances (difficulty sleeping and eating), pessimistic thinking, and suicidal thoughts. Depression has become a common disease problem around the world, affecting over 350 million people (Aldahmashi et al. 2019). In Indonesia, as many as 1522 people suffered from depression as a result of the COVID-19 pandemic (Zahroh et al. 2021). Neurotransmitters such as serotonin, dopamine, and noradrenaline play an important role in mood, desire, and emotion, even influencing impulse control (Margret et al. 2015).

Depression can be treated using Synthetic drugs like Fluoxetine. Fluoxetine (SSRI) is typically used for people suffering from depression to raise serotonin levels (Kaur et al. 2015). However, fluoxetine has side effects such as sweating, asthenia, insomnia, diaphoresis, tremor, sexual dysfunction, increased risk of bleeding, and dry mouth (Tarleton et al. 2016). In Malay culture, areca nuts are always used in a traditional event called "menginang".

The combination of synthetic drugs and herbal plants has been carried out by in vivo, but the mechanism of the additive interaction is unknown (Kaur et al. 2015). In silico approach possibly solves this issue. Previously, in silico studies to predict drug candidates as antidepressants have been carried out with Swiss ADME analysis, molecular docking (Sirait and Novianty 2022; Ningsih and Novianty 2020; Maylinda

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and Novianty 2021; Riryn Novianty 2023), and molecular dynamics simulations (Ananta and Novianty 2022.). The molecular docking of fluoxetine with the areca nut's active compound is a novel feature of this research. Areca nut has a few active compounds such as arecoline, homoarecoline, and guvacoline which can be used as oral drugs (Peng et al. 2015).

Furthermore, the most appropriate strategy for designing an antidepressant is to inhibit the Mnoamine oxidase A (MAO-A) enzyme because it will increase the concentration of neurotransmitter (Chu 2001; Stahl 2013). Furthermore, these compounds of Areca nut can inhibit MAO-A activity by in vivo (Ramsay 2013; Boucher and Mannan 2002). Various studies included behavioural in animal (acute and sub-chronic forced swim tests) anf biochemical (MAO-A and their metabolite levels using high performance liquid chromatography) are done to look into the potential antidepressant efficacy of Areca nut ethanol extract and its various fractions (Dar and Khatoon 1997).

Recently, in silico approach using natural compounds has been carried out (Novianty et al. 2021) However, in silico study about a combination of synthetic drugs and natural compounds has not been observed. Therefore, this study was conducted to determine the effectiveness of areca nut's active compounds combined with fluoxetine as a recent antidepressant drug

2. Methods

2.1. Materials and Instrumentals

Bahan This study was conducted by molecular docking method using a laptop (ASUS Intel® core i3-7020Li, 2.3 GHz, RAM 4.00 GB). The software used in this study are ChemDraw Ultra 13.0, ChemSketch, AutoDock Vina, and BIOVIA Discovery Studio Visualizer (DSV).MAO-A target protein (2Z5Y) and serotonine precursor (2NW8), areca nut's chemical formula (arecoline, guvacoline dan homoarecoline) and fluoxetine chemical formula was obtained from protein data bank.

2.2. Experimental Procedure

2.2.1. Synthesis reaction of areca nut's compound and fluoxetine

The synthesis reaction was drawn using ChemSketch software. The reactions obtained from the combination of compounds shown below.

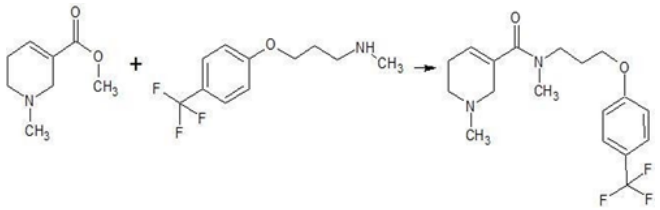

Figure 1. The chemical reaction of Arecoline with Fluoxetine (Code: AF)

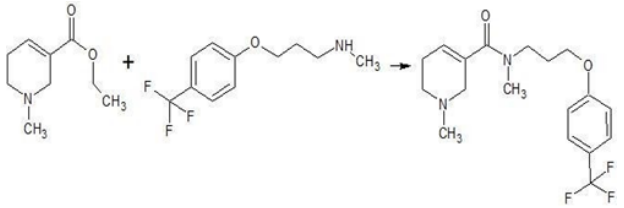

Figure 2. The chemical reaction of Homoarecoline with Fluoxetine (Code: HF)

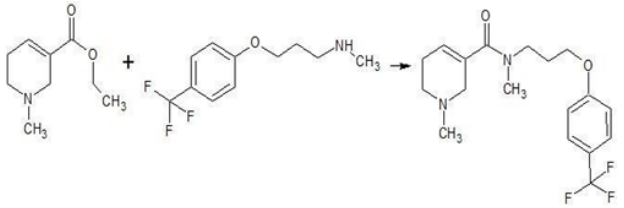

Figure 3. The chemical reaction of Guvacoline with Fluoxetine (Code: GF)

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2.2.2. Validation of redocking on native protein (2Z5Y dan 2NW8)

The 3D structure of 2Z5Y protein (MAO-A protein) and 2NW8 protein (serotonin precursor) was validated by redocking using DSV. Water molecules and other molecules bound to the original protein as well as the native ligands of the protein are removed, and the file is saved in ".pdb" format. Subsequently, the original ligand is processed by eliminating the protein and other molecules from the native protein. Furthermore, the original ligand is saved in the form of ".pdb" format.

2.2.3. Protein and ligand preparation

The molecular structure of the combination compound with codes AF, HF, and GF was drawn using ChemDraw Ultra 13.0 and saved in "protein data bank" format. The protein structure was downloaded from the www.pdb.org website in PDB format (PDB ID: 2Z5Y), then water molecules and initial ligands on the protein were eliminated and the determination of the active site of the 2Z5Y receptor using DSV. The same is done with protein 2NW8.

2.2.4. Docking simulation via Autodock Vina

Before doing the docking simulation, it is necessary to prepare AF, HF and GF ligands by increasing 6x torsion tree and saving them in .pdbqt format. The same is done with fluoxetine.Receptor preparation was carried out by validating and dismissing all protein components (native ligands and water molecules). Hydrogen is added and make a the receptor in a polar condition. Files are saved in "pdbqt" format. Next, a grid box is done by setting the grid spacing to 1 Å and the grid points x, y, z are arranged so that they can contain the active protein site. Grid point on protein 2Z5Y, are x = 104; y = 96 and z = 74. Whereas in 2NW8 protein, position x = 68; y = 84 and z = 84. The docking procedure is claimed valid because from 3 docking experiments, the same value is obtained (Purwaniati 2020).

2.3. Data Analysis

The docking result was interpreted via command prompt application with "C:\Vina>Vina –config config.txt –log log.txt" settings. Then, press enter. So, the docking result will interpret in the command prompt and automatically saved in "output.pdbqt"format

3. Hasil dan Pembahasan

3.1. Molecular Docking Between Fluoxetine and Areca Nut Compounds with MAO-A Protein

Table 1. Molecular docking result of ligands with MAO-A

Ligands	Binding Affinity (kcal/mol)	Hydrogen Bonding	Hydrophobic and Van Der Waals Interactions
Fluoxetine	-9.1	MET445, SER24, THR435, ILE23, ARG51, CYS406	TYR69, TYR444, GLY443, THR52, ALA448, GLY22, GLY66, GLY67, TYR407
AF and HF	-7.1	THR 205	PHE112, PRO114, ALA110, HIS488, TYR124, ASN125, TYR204, TRP128
GF	-7.6	ALA 44	VAL244, THR24, GLY21, GLU43, TYR402, GLY20, LYS280, ILE273, TYR402, LEU277

The result of molecular docking of ligands with MAO-A (25ZY) protein are shown in Table. 1. It was found that fluoxetine has a bond free energy value of -9.1 kcal/mol and RMSD value of 0.000. The docking results showed that fluoxetine could bind to 15 amino acid residues on the active site of the receptor, namely MET445, SER24, THR435, ILE23, ARG51, CYS406, TYR69, TYR444, GLY443, THR52, ALA448, GLY22, GLY66, GLY67, TYR407. Fluoxetine interacts with receptors via hydrogen bonding with MET445, SER24, THR435, ILE23, ARG51, CYS406 residues.

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The drug effectiveness was observed from its bond free energy and RMSD value. Bond free energy is the energy required for initiating intermolecular interactions and complex formation between ligands and receptors. The bond free energy expresses the amount of a ligand bound to the receptor. If the bond free energy value is small, then the bond is stronger. Meanwhile if the bond free energy value is large, the bond is getting weaker and possible to break the loose (Weni et al. 2020). The difference from the bond-free energy value is based on the protein residue that interacts with the ligand. RMSD used to measure the difference between the predicted value and the observation value. The RMSD value is said to be good if ≤ 2 Å (Kumer et al. 2021) If the deviation bigger, then the prediction error is bigger too. So, the best bond free energy value from the bonding results of each ligand is the one that has an RMSD value = 0.

The combination of AF (Arecoline + fluoxetine) and HF (Homoarecoline + fluoxetine) has a bond free energy value -7.1 kcal/mol and RMSD value 0.000. The docking results showed that the combination of AF and HF did not bind to amino acid residues on the receptor's active site. The combination of AF and HF interacts with receptor via hydrogen bonding with THR205 amino acid residue. The combination of GF (Guvacoline + fluoxetine) has a bond free energy value -7.6 kcal/mol and an RMSD value of 0.000. The docking results showed that the GF combination did not bind to the amino acid residue on the receptor's active site. Combination of GF interacts with receptor via hydrogen bonding with ALA44 amino acid residue.

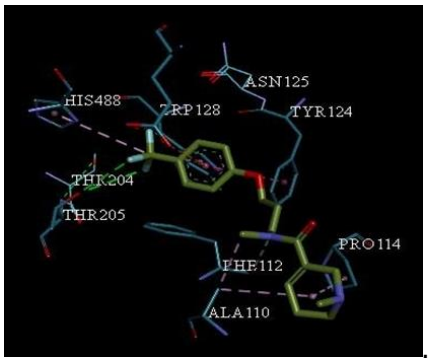

Figure 4. 3D Visualization of Interaction between AF and HF with Amino Acid Residue in 2Z5Y Protein

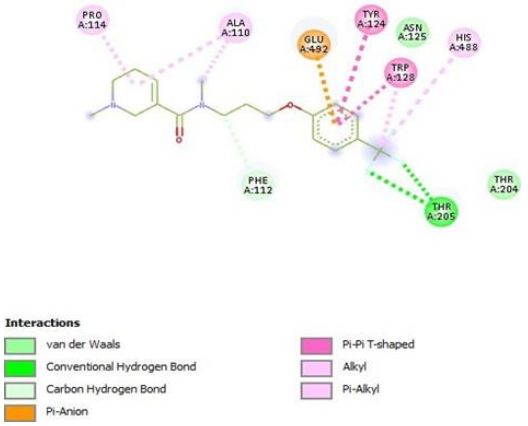

Figure 5. 2D Visualization of Interaction between AF and HF with Amino Acid Residue in 2Z5Y Protein

The drug-receptor bond interaction based on the results of 3D and 2D visualization of MAO-A protein which illustrated in Figure 4 and Figure 5 with AF and HF compounds consisting of hydrogen bonds (THR205), van der walls bonds (THR204), phi-anionic bonds (GLU492), C-H bonds (PHE112), pi-pi T-shaped bonds (TYR124 and TRP228), alkyl activators (ALA110 and PRO114) and pi-alkyl bonds (HIS488).

Meanwhile, in GF compounds (Figure 6 and Figure 7), there are hydrogen bond interactions (ALA44), van der Walls bonds (VAL244, THR245 and GLY21), halogen bonds (GLU43), pi-sigma bonds (TYR402), C-H bonds (GLY20, LYS280), phi-sigma bonds (ILE273), pi-pi T-shaped bonds (TYR402), alkyl bonds (LEU277).

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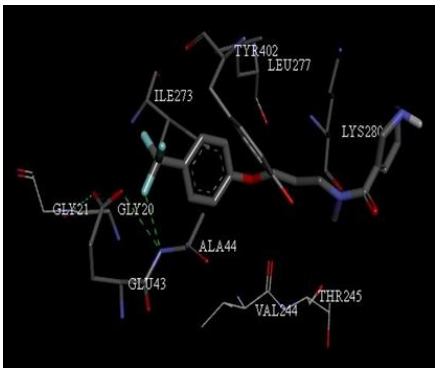

Figure 6. 3D Visualization of Interaction between GF with Amino Acid Residue in 2Z5Y Protein

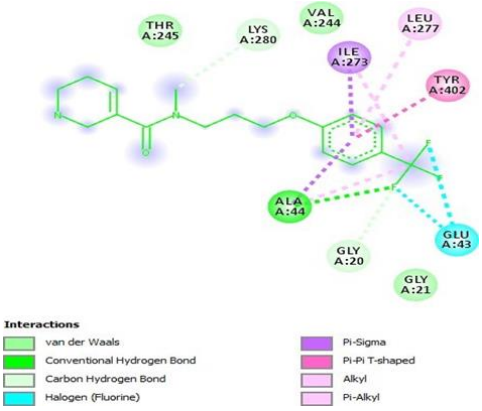

Figure 7. 2D Visualization of Interaction between GF with Amino Acid Residue in 2Z5Y Protein

3.2. Molecular Docking Between Fluoxetine and Areca Nut Compounds with Serotonin Precursors

Table 2. Molecular docking result of ligands with Serotonin

Ligands	Binding Affinity (kcal/mol)	Hydrogen Bonding	Hydrophobic and Van Der Waals Interactions
Fluoxetine	-8.5	Ser 123	LEU 263, VAL 244, LEU 105, THR 243, VAL 247, PHE 51, TYR 113, ILE 248, GLY 125, LEU 108, LEU 120, SER124, THR 254, GLY 253,SER 257
AF and HF	-6.3	-	TYR 113, ILE 248, PHE 51, VAL 247, VAL 244, LEU 263, SER 124, SER 123
GF	-8.8	-	GLY 253, SER 257, VAL 244, TYR 113, ILE 248, VAL 247, PHE 51, LEU 105, LEU 108, THR 243, SER 124, GLY 125

The result of molecular docking of ligands with Serotonin (2NW8) protein are shown in Table 2. Based on the

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docking result between antidepressant compounds and serotonin precursors, it was found that fluoxetine has a bond-free energy value of -8.5 kcal/mol and an RMSD value of 0.000. The docking results showed that fluoxetine could bind to 16 amino acid residues on the receptor's active site, namely LEU263, VAL244, LEU105, THR243, VAL247, PHE51, TYR113, ILE248, GLY125, LEU108, SER123, LEU120, SER124, THR254, GLY253, SER257. Fluoxetine interacts with the receptor via hydrogen bonding with the SER123 amino acid residue.

The combination of AF (Arecoline + fluoxetine) and HF (Homoarecoline + fluoxetine) has a bond-free energy value of -6.3 kcal/mol and an RMSD value of 0.000. The docking results showed that the combination of AF and HF binds to 8 amino acid residues on the receptor's active site, namely TYR113, ILE248, PHE51, VAL247, VAL244, LEU263, SER124, SER123. The combination of AF and HF does not interact with the receptor via hydrogen bonding. The combination of GF (Guvacoline + fluoxetine) has a bond-free energy value of -8.8 kcal/mol and an RMSD value of 0.000. The docking results showed that the combination of GF binds to 11 amino acid residues on the receptor's active site, namely GLY253, SER257, VAL244, TYR113, ILE248, VAL247, PHE51, LEU105, LEU108, THR243, SER124, GLY125.

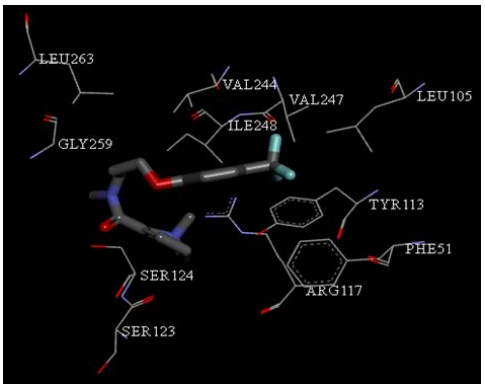

Figure 8. 3D Visualization of Interaction between AF and HF with Amino Acid Residue in 2NW8 Protein

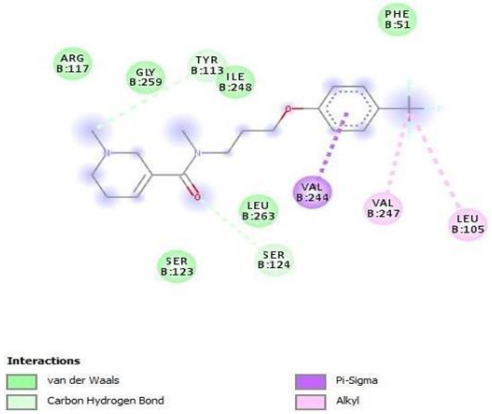

Figure 9. 2D Visualization of Interaction between AF and HF with Amino Acid Residue in 2NW8 Protein

According to the 3D and 2D visualization of the serotonin precursor protein in Figure 8 and Figure 9 with the combination compound AF, HF and GF, there is no hydrogen bond. Molecular interactions on the ligand receptor are not only through hydrogen bonds but also through electrostatic interactions and hydrophobic interactions that contribute to the value of the bond energy (ΔG ligand-receptor) (Arwansyah et al. 2014). The interaction contained in the combination of AF and HF compounds with serotonin precursor proteins, namely van der Walls bonds (ARG117, GLY259, ILE248, LEU263, SER123), C-H bonds (SER124 and TYR113), pi-sigma bonds (VAL244), alkyl bonds (VAL247 and LEU105).

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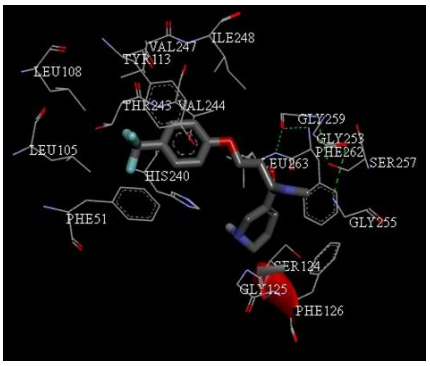

Figure 10. 3D Visualization of Interaction between GF with Amino Acid Residue in 2NW8 Protein

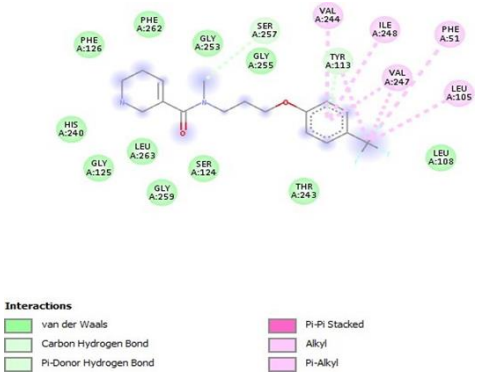

Figure 11. 2D Visualization of Interaction between GF with Amino Acid Residue in 2NW8 Protein

Meanwhile, in GF combination compounds (Figure 10 and Figure 11) there are van der Walls bonds (PHE126, PHE262, GLY253, GLY255, LEU108, THR243, SER124, GLY259, LEU263, GLY125, HIS240), C-H bonds and pi-donor hydrogen bonds (SER257 and TYR113), and alkyl bonds (VAL244, ILE248, PHE51, LEU105).

4. Conclusion

Based on the interaction of antidepressant compounds with MAO-A protein, fluoxetine has the smallest binding free energy value compared to AF, HF and GF compounds. It indicates that fluoxetine is more effective than the AF, HF and GF. Meanwhile, in the interaction of antidepressant compounds with serotonin precursors, GF compound has the smallest bond free energy value compared to AF, HF and fluoxetine. It indicates that GF is more effective than AF, HF and fluoxetine.

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