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Molecular Docking of Gallic Acid and Its Derivatives as the Potential nNOS Inhibitors

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Abstract

The global prevalence of anxiety and depression rates have increased by 25% due to the impact of the COVID-19 pandemic. Depression can occur due to an increase in NO produced by the nNOS enzyme. Gallic acid and its derivatives can be obtained from nature and have various biological activities. This study aimed to determine the potential of gallic acid and its derivatives as nNOS inhibitors using the molecular docking method with parameters of binding energy values, RMSD values, and specific binding to amino acid residues. The results showed that gallic acid, 4-O-methyl gallic acid, and epigallocatechin gallate had bond energies of -1.87; -2.36; and -0.12 kcal/mol, respectively. Compared to the standard ligand, which had binding energy of -2.84 kcal/mol, gallic acid 4-O-(6-galloyl glucoside) had binding energy of -4.12 kcal/mol. Based on these results, gallic acid 4-O-(6-galloyl glucoside) can potentially inhibit nNOS.

1. Introduction

As a world health authority, the World Health Organization (WHO) announced Coronavirus Disease 2019 (COVID-19) as a global pandemic on 11th March 2020. Millions of people worldwide have been affected by the COVID-19 pandemic [1]. According to a scientific report released by WHO in March 2022, the global prevalence of anxiety and depression increased by 25% due to the impact of the COVID-19 pandemic. Meanwhile, mental disorders and depression in Indonesia increased by 6.5% nationally, mainly due to social restrictions and job loss. This increase in depression rates has prompted countries worldwide to include mental health and psychosocial support as a part of their COVID-19 response plans [2].

Psychological factors such as stress, depression, loneliness, and unhealthy behaviors can interfere with the immune system's response to vaccines. Inflammation is one of the body's responses that appear after vaccination which is characterized by fever, muscle aches, and fatigue. This is a good sign because the increase in temperature creates a less favorable environment for the virus and stimulates the body to produce more immune cells. However, based on previous studies, the inflammatory response to vaccination is higher and lasts longer in individuals with depression [3]. This chronic inflammation causes vaccines to not work optimally in forming antibodies needed by the body [4].

Although there are numerous varieties of antidepressants available, some negative effects persist. For instance, selective serotonin reuptake inhibitors (SSRIs) and fluoxetine, most commonly prescribed to treat a severe depressive disorder, have some side effects. Common side effects include anxiety, nausea, vomiting, dry mouth, dizziness, and visual disturbances. Some patients also have serious side effects, such as sexual dysfunction, suicidal ideation, tachycardia, insomnia, and anorexia [5]. Therefore, regarding tolerability and safety levels, researchers are increasingly concerned with discovering and developing antidepressants in traditional herbal medicines [6].

Depression can occur due to several mechanisms. The monoamine hypothesis has long been used in

developing antidepressants [7]. The increase in NO produced during neuroinflammation can lead to brain dysfunction and diseases, such as depression and anxiety [8]. NO is synthesized from L-arginine by three isoforms of the enzyme nitric oxide synthase (NOS), namely neuronal (nNOS), endothelial (eNOS), and induction (iNOS). The nNOS enzyme is prevalent in several brain regions involved with stress and depression—including the hippocampus, hypothalamus, locus coeruleus, and dorsal raphe nuclei. Reducing NO levels by blocking NOS enzymes in the brain can produce an antidepressant effect [9].

Gallic acid has various bioactivities such as antioxidant, anti-inflammatory, anti-microbial, anti-cancer, antineoplastic, antiviral, and antidepressant effects, indicating that it can increase serotonin levels [10]. Gallic acid derivative compounds have high antidepressant-like activity if they have higher lipophilicity, as indicated by a methyl group [11]. Gallic acid derivatives such as epigallocatechin are commonly found in tea leaves, such as green tea, affecting anxiety and depression [12]. The presence of a galloyl group is known to have the activity to inhibit NO production [13].

This study aimed to predict its activity as an antidepressant through the nNOS mechanism using the molecular docking method. Based on binding energy, this method can predict bond conformation in position, type, and affinity. This prediction plays a role in developing compounds that are assumed to have a biological activity to be employed as reference compounds for further drug development [14].

2. Methodology

2.1. Tools and Materials

In this study, the hardware used was a Linux-based operating system (OpenSUSE Leap 15.0) with Intel (R) Core™ i3-7100, CPU @ 3.90Ghz, 8 GB of RAM 64-bit. The software was AutoDock 4.2.6 [15], UCSF Chimera [16], GaussView 5.0.8 [17], Gaussian 09W [18], Open Babel GUI [19], and Discovery Studio Visualizer [20], which were accessed via hardware facilities at the Computational Chemistry Laboratory, Faculty of Mathematics and Natural Sciences, Gadjah Mada University.

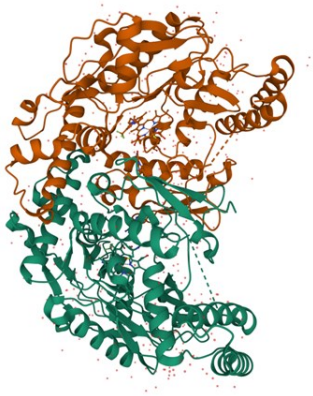
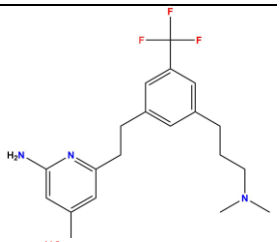
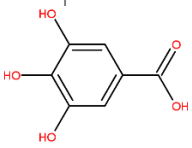
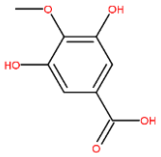
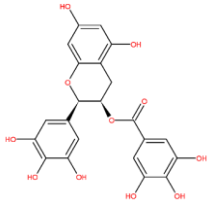
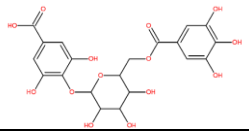


Figure 1. Structure of nNOS protein

The materials needed in this study include the molecular structure of gallic acid derivatives and the macromolecular structure of neuronal nitric oxide synthase (nNOS) with PDB ID code 6AV2 obtained through the RSCB.org database and shown in Figure 1.

Table 1. Structure of standard and proposed ligands

Ligand	IUPAC	Structure
BY7 (standard ligand)	6-(2-{3-[3-(dimethylamino)propyl]-5-(trifluoromethyl)phenyl}ethyl)-4-methylpyridin-2-amine	
Gallic acid	3,4,5-trihydroxy benzoic acid	
4-O-methyl gallic acid	3,5-dihydroxy-4-methoxy benzoic acid	
Epigallocatechin gallate	[(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzoate	
Gallic acid 4-O-(6-galloyl glucoside)	3,5-dihydroxy-4-((3,4,5-trihydroxy-6-(((1-(3,4,5-trihydroxyphenyl)vinyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)benzoic acid	

2.2. Bioavailability analysis and preparation of standard ligand, proposed ligands, and proteins

The proposed gallic acid derivatives were analyzed for their properties related to the feasibility of oral drugs based on Lipinski rules using Molsoft Drug-Likeness (https://molsoft.com/mprop/). Furthermore, the proposed gallic acid derivatives were sketched in GaussView, and geometric optimization was done in Gaussian using the DFT B3LYP method with a 6-311G++ (d,p) basis set. The B3LYP method has been reported to perform well on organic molecules. The basis set was added by a diffusion function (+) which is a spherical harmonic that allows the calculation of electrons with the probability of being far from the nucleus, and the addition of a polarization function (** or d,p) that can provide better flexibility for the deformed wave function, thus providing a more accurate geometry and vibrational frequency [21].

The optimized ligand compound molecule was then converted to .mol2 format file using the Open Babel GUI, and the ligand is ready to proceed to the following step. The nNOS macromolecule previously downloaded on RCSB.org was then prepared using UCSF Chimera by separating the protein and its standard ligand. Chain A protein was selected from the nNOS (6AV2) protein, and

the non-standard residue was removed. The charge and hydrogen atoms were then added using the Dock Prep feature to obtain an empty protein that ignores the presence of water in the .pdb extension. Standard ligands were also prepared and saved in .mol2 file format.

2.3. Docking of proteins and standard ligand

The docking of proteins and standard ligand was performed using the AutoDock4 Tools software. The grid box size was 60 × 60 × 60 Å^3 at coordinate x = 122.02; y = 244.24; z = 359.302 with a grid spacing of 0.375 Å. The catalytic residue GLU 597 served as the main amino acid target in the process of nNOS molecular docking. The AutoDock4 parameter was set at 100 GA runs, 2,500,000 energy evaluations, and 150 population sizes. The molecular docking simulation was done using the Lamarckian Genetic Algorithm Local Search (GALS) calculation. The docking method is valid when the redocking between the standard ligand (code: BY7) and the nNOS receptor shows an RMSD value of 2 Å so that the docking method can be applied to proposed ligands [22]. The best conformation of the standard ligand was determined by the lowest binding energy (BE) value and RMSD ≤ 2 Å.

The standard ligand (BY7) redocking was performed to determine the target protein's active site. The conformation and position of the docked standard ligand would be a reference for the following proposed ligands docking process. The standard ligand redocking had an RMSD value of 0.61, which means that the docking method employed in this study is valid and the parameter settings used have fulfilled the validation criteria. Therefore, the method and parameter settings can be used to dock the proposed ligand molecules. The overlay of the standard ligands before and after docking is shown in Figure 2.

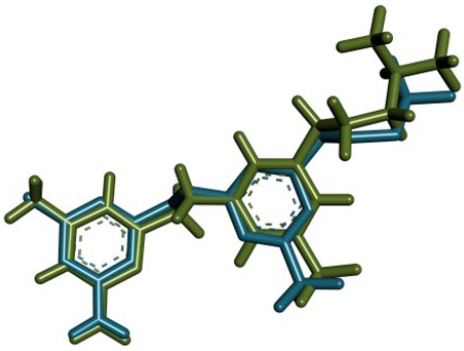


Figure 2. Overlap of standard ligands before (green) and after docking (blue)

The docking of gallic acid-derived ligand molecules was achieved by equating the conformation and position coordinates of the gallic acid-derived ligands with the standard ligands using the dejaVu GUI feature on AutoDock4 Tools. Gallic acid-derived ligands were saved as .pdbqt files. Furthermore, the docking process for gallic acid-derived ligands on macromolecules used the same parameters, grid box size, and grid box coordinates as standard ligands. The best conformation of the proposed ligands was selected based on the lowest binding energy value, RMSD lower than 2 Å, and the interaction formed with Glu 597 residue. The conformational results of the ligand-receptor complex were stored in .pdb format. Docking results in .pdb format were then visualized using the Discovery Studio Visualizer (DSV) software. Visualization was done in 3D and 2D diagrams to view the protein-ligand interactions.

2.4. Analysis of potential inhibitory properties

The potential antidepressant properties of the proposed ligands were analyzed using the molecular docking results with AutoDock4. The ligand was docked to the binding pocket of nNOS protein. The parameters used for the analysis were binding energy, RMSD value, and the interaction formed with the amino acid residue of the receptor.

The binding energy demonstrates the stability of the ligand to protein, which also reveals that the bond can occur spontaneously—the lower the binding energy value, the stronger and more stable the bonding. The type of hydrogen bond formed was used to analyze the interaction mechanism. RMSD was also reviewed since it may quantify how much the protein-ligand interaction in the crystal structure changes before and after docking. The docking method and parameters are valid if the RMSD value is 2 Å [23].

3. Results and Discussion

3.1. Bioavailability analysis of the proposed ligands oral drug

This research tested four proposed ligands of gallic acid derivative docked to nNOS protein. The proposed ligands include gallic acid, 4-O-methyl gallic acid, epigallocatechin gallate, and gallic acid 4-O-(6-galloyl glucoside). The bioavailability analysis of oral drugs based on Lipinski's rules using Molsoft Drug-Likeness is shown in Table 2. The drug-likeness model score of the proposed ligands is shown in Figure 3.

Table 2. Results of analysis using Molsoft

Ligand	Molecular weight (Da)	HBA	HBD	Log P	Lipinski's rule deviation	Drug-likeness score
Gallic acid	170.02	5	4	0.78	0	-0.22
4-O-methylgalic acid	184.04	5	3	0.95	0	-0.70
Epigallocatechin gallate	458.38	11	8	1.44	2	0.88
Gallic acid 4-O-(6-galloyl glucoside)	484.37	14	9	-0.38	2	0.23

Lipinski's rule is essential in developing and discovering a candidate orally administered drug compound. The five rules (rule of five) of Lipinski include a molecular weight of not more than 500 Daltons, high lipophilicity with a log P value of not more than 5, hydrogen bond donors not more than 5, bond acceptors not more than 10, and the molar refractivity is between 40–130 [24]. Molecules with molecular weights greater

than 500 Daltons would have difficulty penetrating through the digestive and epidermal membranes [22]. The log P value describes the lipophilicity of the compound [25]. A compound with a log P value greater than five may potentially be toxic due to its low solubility in water. The substance is, therefore, difficult to eliminate and may accumulate in the body [26]. The absorption of a compound is determined by its solubility and permeability. The number of hydrogen bonds indicates an essential parameter in drug permeability [27].

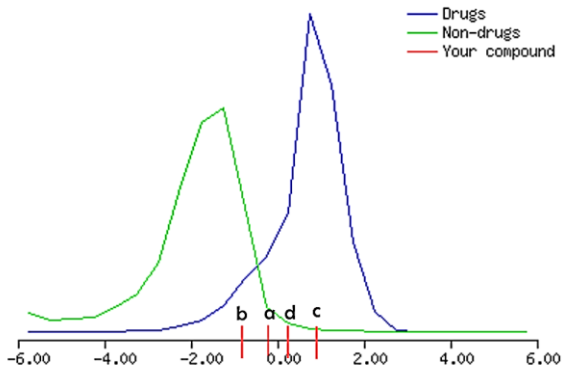


Figure 3. Drug Likeness Model Score (a) Gallic acid, (b) 4-O-methyl gallic acid, (c) Epigallocatechin gallate, (d) Gallic acid 4-O-(6-galloyl glucoside)

The value of the drug-likeness score represents the structural similarity of the proposed ligands to drug compounds discovered previously and contained in the system database. Molsoft's analysis calculated the score's drug-likeness model representing the combined effect of physicochemical, pharmacokinetic, and pharmacodynamic properties. The blue curve indicates that the compound is categorized as having drug-like properties, while the green curve does not show drug-like properties [27].

Epigallocatechin gallate and gallic acid 4-O-(6-galloyl glucoside) did not meet the requirements for hydrogen bond donor and acceptor stipulated in Lipinski's rule as an oral drug. This can indicate that both compounds have poor absorption. On the other hand, gallic acid and 4-O-methyl gallic acid comply with Lipinski's rule. However, both compounds are not categorized as oral drug-like since their drug-likeness values are less than 0. It can be said that all the proposed ligands have low oral bioavailability. Theoretically, 100% bioavailability in the blood can be achieved if the active compound is administered directly by the intravenous route [28]. The method of forming micro-sized particles also increases bioavailability, so further research is required to develop this drug compound [29].

3.2. Molecular Docking

Interaction studies were done by docking gallic acid molecules and their derivatives as an alternative to potential antidepressants. This study was carried out by docking the molecular structure of gallic acid and several of its derivatives as ligands to the nNOS protein (code: PDB 6AV2). The proposed ligands used were geometrically optimized to obtain a stable geometry of a compound structure, and the molecules were docked to the prepared receptor. The results of each docked proposed ligand were taken based on the lowest binding energy value and Root Mean Square Deviation (RMSD) ≤ 2 Å. The specified RMSD value represented the change in conformation or distance from the molecular reference structure to the molecular structure resulting from a positional change. The smaller the RMSD value, the closer the position of the standard ligand resulting from molecular docking to the standard crystallographic ligand [30].

3.3. Gallic acid and its derivatives as nNOS inhibitors

High levels of NO in the brain can be lowered by nNOS inhibition. The standard and proposed ligands were docked to nNOS protein, and the results were analyzed to determine the nNOS inhibition. The molecular docking results of standard and proposed ligands are shown in Table 3.

Table 3. Docking results of standard ligands and proposed ligands

Ligand	Binding energy (kcal/mol)	RMSD (Å)	Hydrogen bonds	Number of residues	Amino acid residue
BY7 (standard ligand)	-2.84	0.61	2	9	**GLU 597, ARG 608, , TRP 592,** ASP 602, PHE 589, PRO 570, ARG 486, MET 594
Gallic acid	-1.87	1.93	3	3	**GLU 597, ASP 602**
4-O-methyl gallic acid	-2.36	1.83	4	4	**GLU 597, ASP 602,** GLN 483
Epigallocatechin gallate	-0.12	1.26	7	8	**GLU 597, ASP 602, PRO 570,** TYR 593, ASN 574, SER 482, VAL 572
Gallic acid 4-O-(6-galloyl glucoside)	-4.12	1.75	7	7	**GLU 597, ARG 608, , TRP 592,** GLN 483, GLY 591, PRO 570

According to these results, the 4-O-(6-galloyl glucoside) had a binding energy value of -4.12 kcal/mol, followed by 4-O-methyl gallic acid of -2.36 kcal/mol, gallic acid of -1.87 kcal/mol, and epigallocatechin gallate of -0.12 kcal/mol. The gallic acid 4-O-(6-galloyl glucoside) exhibited a more negative binding energy than the other proposed and standard ligand. Therefore, the gallic acid 4-O-(6-galloyl glucoside) interaction with the standard ligand was compared to examine the possible interactions.

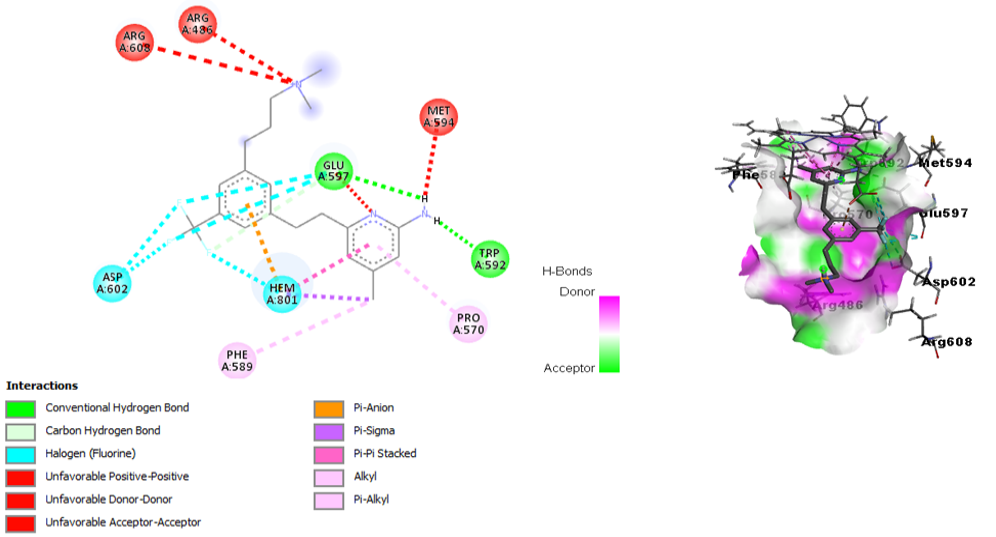


Figure 4. The interaction of the standard ligand with the nNOS receptor

The interaction between residues and standard and proposed +ligands was visualized in 2D and 3D using the Discovery Studio Visualizer. Further discussion would compare the interactions between standard ligands and gallic acid 4-O-(6-galloyl glucoside) on the nNOS receptor, as it was previously mentioned that gallic acid 4-O-(6-galloyl glucoside) had more negative binding energy than standard ligands. A comparison of the interaction of the standard ligand with gallic acid 4-O-(6-galloyl glucoside) is shown in Figure 4.

According to the results of standard ligand binding in Figure 4, it is known that interactions with nine amino acid residues were formed, including GLU 597, TRP 592, ASP 602, PHE 589, PRO 570, ARG 608, ARG 486, and MET 594. These results were used to compare the bound amino acid residues and the type of bond formed with the proposed ligands of gallic acid derivative in inhibiting nNOS protein. All proposed ligands had the same interaction with residue GLU 597.

The docking results of the proposed compound gallic acid 4-O-(6-galloyl glucoside) in Figure 5 show interactions with residues including GLU 597, TRP 592, ARG 608, GLN 483, GLY 591, and PRO 570. The proposed compound gallic acid 4-O-(6-galloyl glucoside) showed more hydrogen bonds to the residue than the standard ligand, indicating that the interaction was formed at a more stable binding site area. The visualization results in Figure 5 demonstrated the similarity of the bound amino acid residues to the standard ligand, such as GLU 597 and TRP 592. Both residues had the same hydrogen bonding type as the standard ligand.

Further analysis in Figure 5 revealed that the gallic acid 4-O-(6-galloyl glucoside) interaction with the nNOS receptor resulted in seven hydrogen bonds, of which two were bound to the catalytic residue of GLU 597. In contrast, the standard ligand in Figure 4 only formed a hydrogen bond in the GLU 597 residue. Since GLU 597 is a catalytic residue directly involved in the catalyzed reaction, the specific bond on that residue needs to be considered [31]. Furthermore, the gallic acid 4-O-(6-galloyl glucoside) produced more hydrogen bonds than the standard ligand, leading to higher conformational stability when interacting with the nNOS receptor. Another similar residue that interacted was ARG 608. The interaction type of the ARG 608 was unfavorable positive-positive in the standard ligand but hydrogen-bonded in gallic acid 4-O-(6-galloyl glucoside). The type of interaction formed was different between the standard ligand and gallic acid 4-O-(6-galloyl glucoside) at residue ARG 608. However, the hydrogen bonding of gallic acid 4-O-(6-galloyl glucoside) has a better type of interaction.

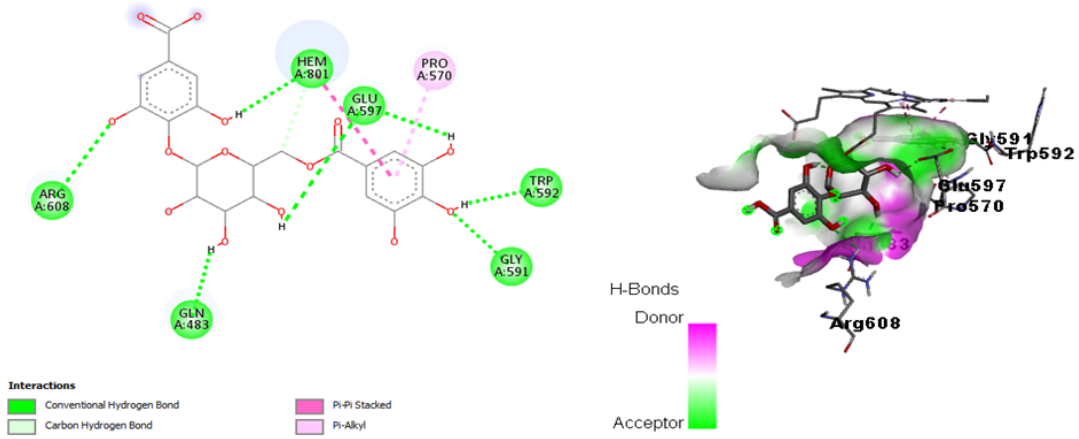


Figure 5. Interaction of gallic acid 4-O-(6-galloyl glucoside) with nNOS receptors

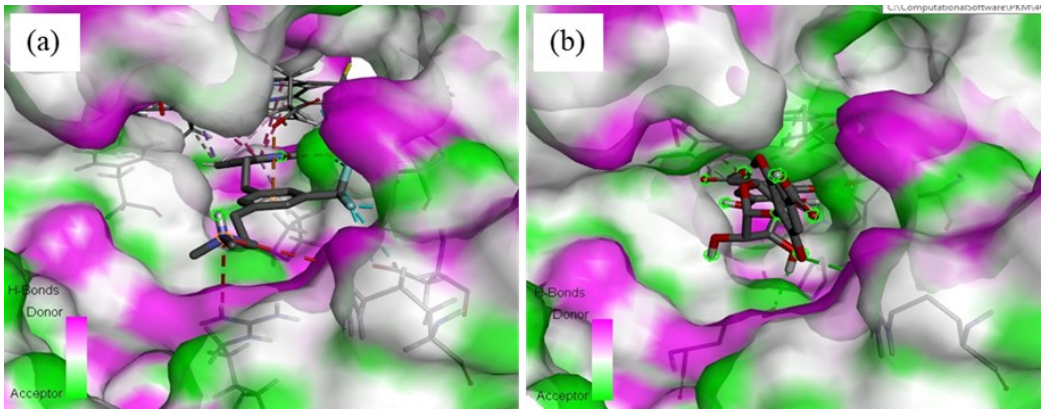


Figure 6. The equal docking position is seen from the same side (a) Standard ligand docking (b) 4-O-(6-galloyl glucoside) docking

The gallic acid 4-O-(6-galloyl glucoside) had the same type of interaction and number of residues when reviewed based on the similarity of interactions formed from the gallic acid 4-O-(6-galloyl glucoside) and the standard ligand to the receptor. Therefore, the gallic acid 4-O-(6-galloyl glucoside) had nearly the same binding position as the standard ligand. The similarity of the docking position is emphasized in Figure 6 when viewed from the same visualization angle. The gallic acid 4-O-(6-galloyl glucoside) exhibited the same biological activity as the standard ligand since it was bound to the identical amino acid residue.

Hydrogen bonding becomes a specific interaction essential in the ligand-receptor interaction process since it contributes to increasing the compound's affinity to the receptor. Hydrogen bonds may form electrostatic interactions or hydrogen donors and acceptors. This is in line with the crystal structure's hydrogen bonding and the docking validation results that the GLU 597 residue is predicted to have a stable interaction.

The analysis showed that gallic acid and its derivatives 4-O-methyl gallic acid and gallic epigallocatechin had specific bonds with GLU 597 residue. However, these compounds have not demonstrated a good inhibitory potential against nNOS protein because they have higher binding energy than nNOS protein standard ligand. The three compounds have not shown potential biological activity as antidepressants. The gallic acid 4-O-(6-galloyl glucoside) had better inhibitory activity when bound to the nNOS receptor than standard and other proposed ligands of gallic acid derivatives. According to the study, the gallic acid 4-O-(6-galloyl glucoside) deserves further research on its synthesis and conducting molecular dynamics simulations to determine how the compound interacts with water in the body and evaluate its activity in vivo or in vitro.

4. Conclusion

According to the study on gallic acid and its derivatives, gallic acid-4-O-(6-galloyl glucoside) exhibited nNOS inhibitory activity because it has more negative binding energy than the standard ligand and a specific bond with residue GLU 597.

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