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RESEARCH ARTICLE

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Molecular docking of ferulic acid, bakuchiol and niazirin on peroxisome proliferator-activated receptor gamma (PPAR-γ) as anti-diabetic agents

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ABSTRACT

Background: Diabetes mellitus remains one of the most dangerous illnesses worldwide. The PPAR-gamma protein plays a crucial role in lipid and carbohydrate metabolism, making it a key target for diabetes therapy. Research into plant-derived active compounds for diabetes treatment is increasingly important.

Objective: This study aims to evaluate and analyze the interaction of ferulic acid, niazirin, and bakuchiol with the peroxisome proliferator-activated receptor gamma (PPAR-γ) protein using molecular docking.

Methods: Molecular docking was employed to assess the interactions between ferulic acid, niazirin, bakuchiol, and the PPAR-γ protein (PDB ID: 2PRG). The analysis focused on binding free energy values, amino acid residue interactions, the number of hydrogen bonds, and bond distances, comparing these results to those of the native ligand and pioglitazone, a known anti-diabetic drug targeting PPAR-γ.

Results: The binding free energies for the ferulic acid-PPAR-γ, bakuchiol-PPAR-γ, niazirin-PPAR-γ, native ligand-PPAR-γ, and pioglitazone-PPAR-γ complexes were -5.54 kcal/mol, -8.47 kcal/mol, -6.56 kcal/mol, -10.08 kcal/mol, and -9.94 kcal/mol, respectively. The amino acid residue similarity percentages with the native ligand were 18.18% for ferulic acid, 27.27% for bakuchiol, 18.18% for niazirin, and 81.82% for pioglitazone. The native ligand-2PRG and pioglitazone-2PRG complexes exhibited superior hydrogen bond numbers and shorter bond distances compared to the other compounds.

Conclusion: Although bakuchiol showed the most promising interaction among the tested compounds, none surpassed the binding affinity and stability of the native ligand or pioglitazone. Further research is needed to optimize these compounds for potential anti-diabetic therapy.

Keywords: peroxisome proliferator-activated receptor gamma, molecular docking, ferulic acid, bakuchiol, niazirin

Introduction

Diabetes mellitus remains one of the chronic diseases, responsible for the deaths of millions of people worldwide. Indonesia ranks among the top ten countries with the highest prevalence of diabetes globally. In Depok, Indonesia, the number of diabetes cases increased significantly from 21,971 in 2015 to 34,452 in 2016, representing a surge of 12,481 cases in just one year. Additionally, research in a local health center revealed that 71.4% of 77 respondents had elevated blood sugar levels, underscoring the severity of the condition in this region [1]. The rising incidence of diabetes mellitus is linked to lifestyle changes, such as increased consumption of high-glucose and fast foods, reduced physical activity, and sedentary work habits, all of which contribute to elevated blood glucose levels [2].

The PPAR-gamma (PPAR-γ) protein, a nuclear receptor encoded by the PPAR-γ gene, plays a crucial role in regulating glucose and lipid metabolism. It is vital for energy production and lipid synthesis in adipose tissue [3,4]. The PPAR-γ protein comprises several domains,

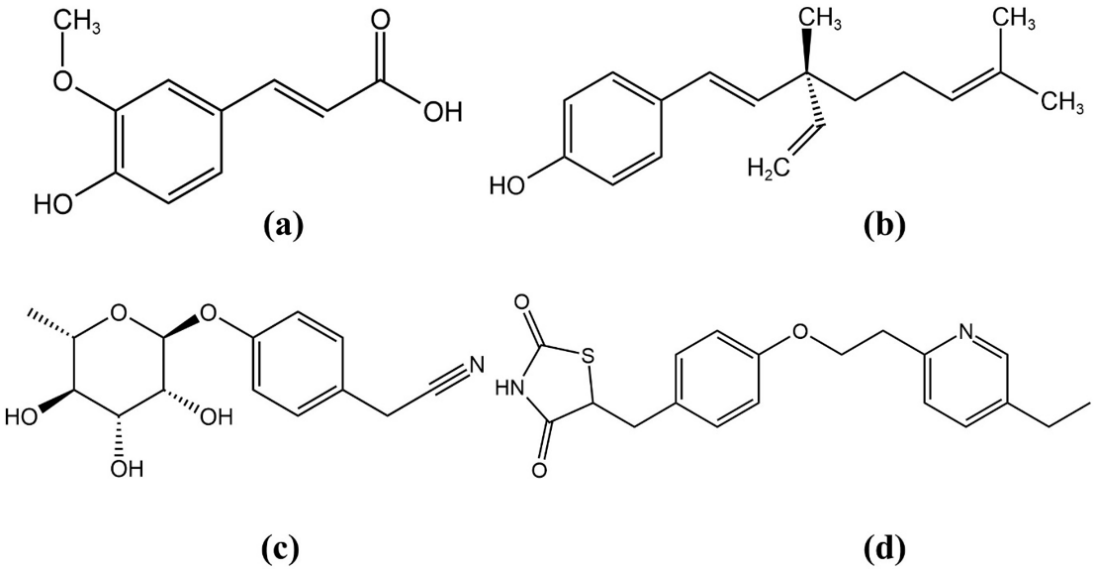

Figure 1. The molecular structures of test compounds. (a). ferulic acid, (b). bakuchiol (c). niazirin and (d). pioglitazone

including the DNA binding domain (DBD) and the ligand binding domain (LBD) [5]. The DBD regulates gene transcription by binding to peroxisome proliferator response elements (PPREs), while LBD is activated when it binds to a ligand, leading to the activation of PPAR- γ [6]. The binding of PPARγ to its ligands, leading to heterodimerization, affects insulin secretion and resistance. Pioglitazone, an anti-diabetic drug, functions as a PPAR-γ agonist. By activating PPAR-γ, pioglitazone modulates the expression of various genes involved in glucose and lipid metabolism, such as glucose transporter type 4 (GLUT4). In addition, the activated PPAR- γ also inhibits the secretion of monocyte cytokines and MMP-9 [7].

Several active compounds in plants, including ferulic acid, bakuchiol, and niazirin, have shown potential therapeutic effects. Ferulic acid, a phenolic compound found in tomatoes, bran, and corn, has demonstrated anti-cardiovascular, antioxidant, anti-cancer, and anti-diabetic properties by lowering blood glucose levels and protecting against neurodegeneration [8]. Bakuchiol, a terpenoid compound, exhibits antioxidant, antibacterial, anti-inflammatory, and anti-cancer activities [9]. Niazirin has been shown to reduce lipid levels and gluconeogenesis, enhance glucose breakdown and lipid oxidation, and act as an anti-inflammatory agent [10]. This study aims to evaluate and analyze the interaction of ferulic acid, niazirin, and bakuchiol with the peroxisome proliferator-activated receptor gamma (PPAR-γ) protein through molecular docking.

Methods

Compounds and protein target preparation

Compounds studied in this research was ferulic acid, bakuchiol, niazirin as well as pioglitazone as positive control (Figure 1). The 3D structures of ferulic acid, bakuchiol, and niazirin were obtained as .mol files from MolView (www.molview.org) and then converted to .pdb files using Avogadro® software. The structures were further optimized using Gaussian® software. The protein target, human peroxisome proliferator-activated receptor gamma (PPAR-γ), with PDB ID 2PRG, was downloaded from the RCSB Protein Data Bank (www.rcsb.org/structure/2PRG).

Molecular docking

Molecular docking was performed using AutoDockTools® software to assess the interactions between ferulic acid, bakuchiol, niazirin, and the native ligand with the 2PRG protein. Validation was conducted by redocking the native ligand, 2,4-thiazolidinedione, 5-[[4-[2-(methyl-2-

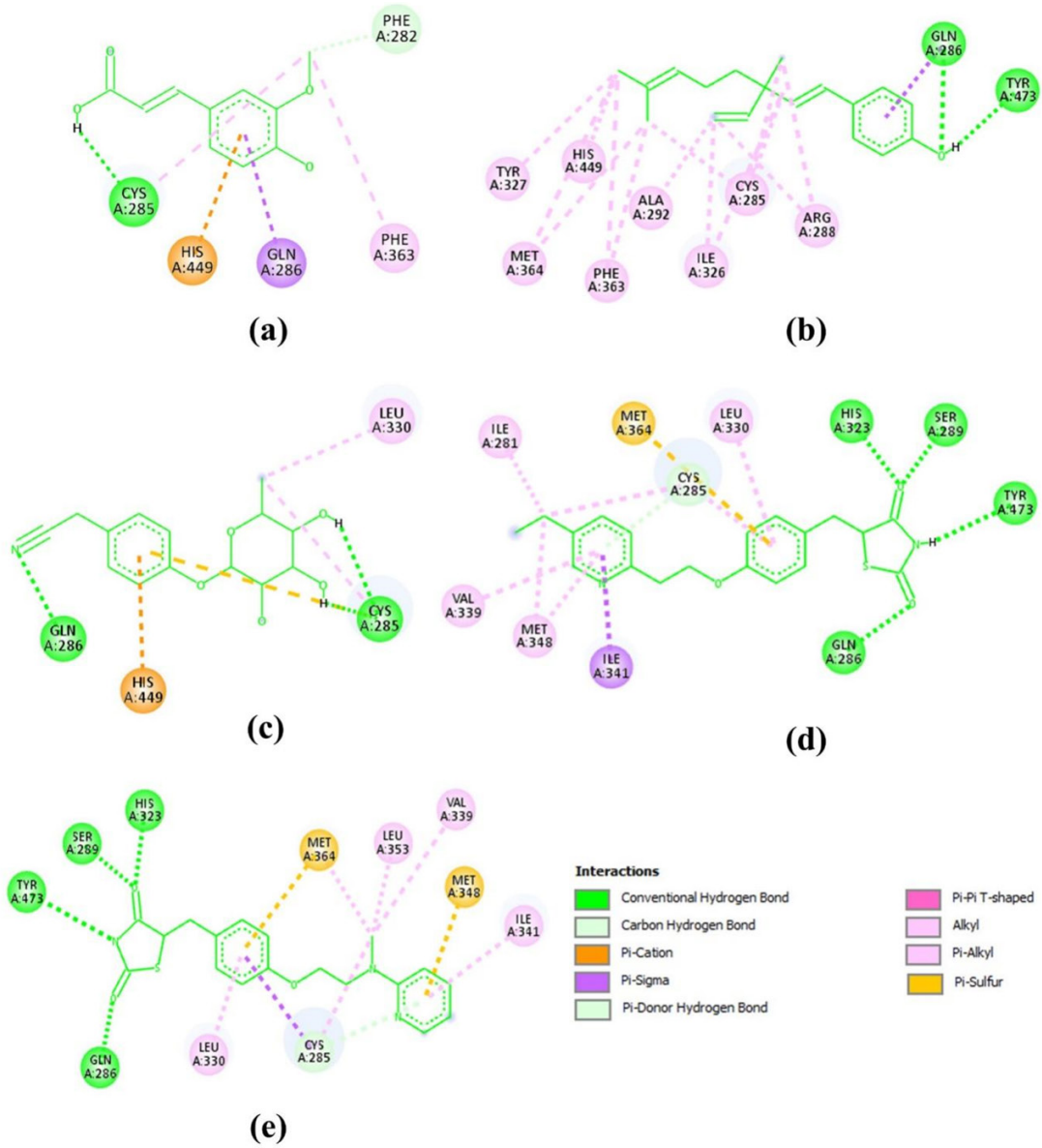

Figure 2. 2D visualization of amino acid residues of compound-protein complex. (a). ferulic acid-PPAR-γ, (b). bakuchiol-PPAR-γ, (c). niazirin-PPAR-γ, (d). pioglitazone-PPAR-γ, and (e). native ligand-PPAR-γ

Table 1. Visualization of amino acid residues for ferulic acid, bakuchiol, niazirin, pioglitazone, and the native ligand binding to the PPAR-γ protein

No	Compounds	Amino acid residues
1	Ferulic Acid	Cys285, His449, Gln286, Phe363, Phe282
2	Bakuchiol	Tyr327, His449, Met364, Phe363, Ala292, Ile326, Cys285, Arg288, Gln286, Tyr473
3	Niazirin	Gln286, His449, Cys285, Leu330
4	Pioglitazone (positive control)	Ile281, Met364, Cys285, Leu330, His323, Ser289, Tyr473, Gln286, Ile341, Met348, Val339
5	Native ligand	His323, Ser289, Tyr473, Gln286, Leu330, Cys285, Ile341, Met348, Val339, Leu353, Met364

pyridylamino) ethoxy] phenyl]methyl]-(9cl) (BRL), to the protein. The docking procedure generated 100 conformations for each ligand. The results were analyzed using Biovia Discovery Studio® software. The docking box was sized at 32 x 28 x 30 with a spacing of 0.375 Å, and the grid center coordinates were x = 50.345, y = -38.214, and z = 19.575.

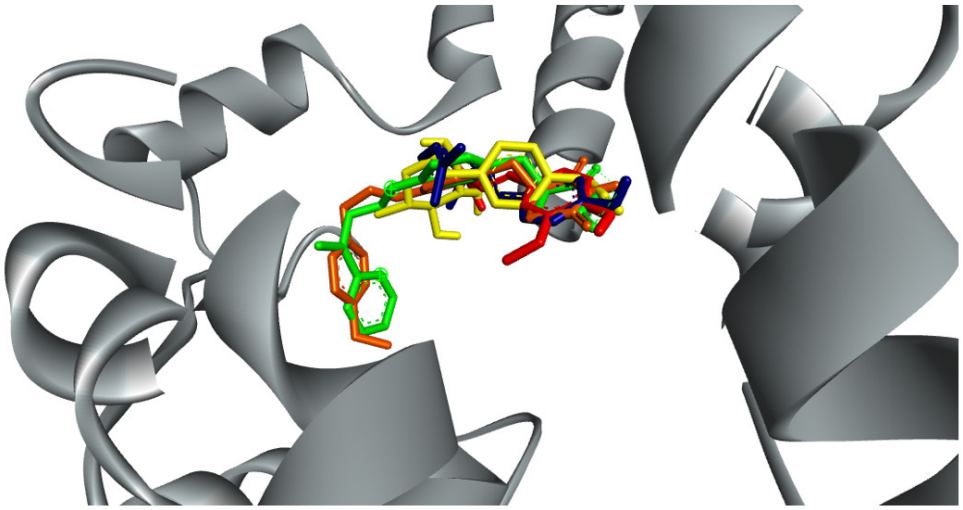

Figure 3. 3D visualization of molecular docking interaction of compounds to the protein. Native ligand (green), ferulic acid (red), bakuchiol (dark blue), niazirin (yellow) and pioglitazone (orange) with PPAR-γ protein

Table 2. Number of hydrogen bond and the their bond distance of compounds-protein interaction

No	Compounds	Number of hydrogen bond	Bond distance (Å)
1	Ferulic acid	2	2.00, 3.19
2	Bakuchiol	2	2.24, 2.25
3	Niazirin	3	2.0, 2.20, 2.10
4	Pioglitazone (positive control)	4	1.94, 1.90, 1.83, 2.49
5	Native ligand	4	1.78, 1.96, 1.85, 3.02

Data analysis

Data analysis involved assessing the root mean square deviation (RMSD) to ensure a validity threshold of less than 2 Å. Additionally, the similarity of amino acid residues bound to the compounds, the number of hydrogen bonds, and bond distances were evaluated using Biovia Discovery Studio® software. The binding free energies of the ligand-protein complexes were also calculated using AutoDock® software.

Results

Molecular docking validation

Validation of the molecular docking process was performed by redocking the native ligand, 2,4-thiazolidinedione, 5-[[4-[2-(methyl-2-pyridylamino) ethoxy] phenyl]methyl]-(9cl) (ID: BRL), to the target protein using 100 conformations. The resulting RMSD value was 1.13 Å, confirming the accuracy of the docking process.

Molecular docking

Molecular docking was conducted for the compounds ferulic acid, bakuchiol, and niazirin with the PPAR-γ protein, using the same box size, spacing, and grid center as in the validation process. The binding free energies were: -10.08 kcal/mol for the native ligand, -5.45 kcal/mol for the ferulic acid, -8.47 kcal/mol for the bakuchiol, -6.56 kcal/mol for the niazirin, and -9.94 kcal/mol for the positive control, pioglitazone. Visualization of the amino acid residues involved in the interactions is presented in Table 1 and Figure 2. Visualization of the three-dimensional of molecular docking interaction of native ligand, the compounds and pioglitazone with the PPAR-γ can be seen on the Figure 3.

Additionally, other parameters such as the number of hydrogen bonds and their bond distances were evaluated, as shown in Table 2.

Among the complexes, bakuchiol had lower binding free energy and greater amino acid similarity to the native ligand compared to ferulic acid and

niazirin. However, the niazirin-PPAR-γ complex had a greater number of hydrogen bonds than both the ferulic acid-PPAR-γ and bakuchiol-PPAR-γ complexes. Bakuchiol shows the highest similarity with the native ligand, followed by pioglitazone and niazirin, while ferulic acid has the least similarity among the tested compounds.

Discussion

In silico methods, such as molecular docking, employed in this study provide valuable insights into the potential anti-diabetic activity of compounds like ferulic acid, bakuchiol, and niazirin. The target protein used in this research was the human peroxisome proliferator-activated receptor gamma (PPAR-γ). The molecular docking process was validated by redocking the native ligand into the 2PRG protein, resulting in an RMSD of 1.13 Å. This value confirms the validity of the docking process, as an RMSD below 2 Å is considered acceptable for reliable docking studies [11].

The molecular docking of ferulic acid, bakuchiol, and niazirin with the PPAR-γ yielded binding free energy values and identified key amino acid residues involved in the interactions. Among the tested compounds, the bakuchiol-PPAR-γ complex exhibited a more favorable binding free energy than the ferulic acid and niazirin, though it was still less favorable than that of the native ligand and pioglitazone. The binding free energy is crucial for evaluating the stability of the interaction between a compound and its target protein, with more negative values indicating stronger and more stable interactions [12].

Regarding amino acid residue similarity, the ferulic acid- complex shared two residues (Cys285 and Gln286) with the native ligand-PPAR-γ complex, resulting in an 18.18% similarity. The bakuchiol-PPAR-γ complex shared three residues (Cys285, Gln286, and Tyr473) with the native ligand, leading to a 27.27% similarity. The niazirin-PPAR-γ complex also shared two residues (Gln286 and Cys285), matching the 18.18% similarity observed for ferulic acid. In comparison, the pioglitazone-PPAR-γ complex (positive control) shared nine residues with the native ligand (Cys285, Leu330, His323, Ser289, Tyr473, Gln286, Ile341, Met348, and Val339), yielding an 81.82% similarity. A higher percentage of shared amino acid residues suggests a more stable interaction with the protein and a greater likelihood of the compound exhibiting similar activity to the native ligand [13].

Additionally, the number of hydrogen bonds and their bond distances were analyzed. The stability of the compound-protein complex is enhanced by a greater number of hydrogen bonds and shorter bond distances. The native ligand-PPAR-γ and pioglitazone-PPAR-γ complexes each formed four hydrogen bonds, with the closest bond distance being 1.78 Å. In contrast, the ferulic acid, bakuchiol, and niazirin complexes formed fewer hydrogen bonds and had longer bond distances, indicating less stable interactions compared to the native ligand and pioglitazone complexes. A stable hydrogen bond is generally characterized by a bond distance of less than 2.7 Å [15].

Based on these molecular docking results, the ferulic acid, bakuchiol, and niazirin complexes with the PPAR-γ protein were less stable and exhibited weaker interactions compared to the native ligand-PPAR-γ and pioglitazone-PPAR-γ complexes, as evidenced by their binding free energies, amino acid residue similarities, and hydrogen bond analyses.

The limitation of this molecular docking study is that it does not account for the dynamic nature of ligand-protein interactions over time. Further research, including molecular dynamics simulations, is needed to evaluate these interactions more comprehensively. Additionally, in vitro and in vivo studies are necessary to validate the potential of ferulic acid, bakuchiol, and niazirin as anti-diabetic agents targeting PPAR-γ.

Conclusion

Based on these molecular docking results, the ferulic acid, bakuchiol, and niazirin complexes with the PPAR-γ protein were less stable and exhibited weaker interactions compared to the native ligand-PPAR-γ and pioglitazone-PPAR-γ complexes, as

indicated by their binding free energies, amino acid residue similarities, and hydrogen bond analyses. Further research, including molecular dynamics simulations, as well as in vitro and in vivo experiments, is necessary to validate the potential of these compounds as PPAR-γ agonists.

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Declaration of interest

None.

Author contributions

Conceptualization, AHS; Methodology, AHS, S, ISS; Investigation, RF, S; Writing – Original Draft, AHS, S, ISS, RF; Writing – Review & Editing, AHS, S, ISS, RF.

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