MEDFARM: Jurnal Farmasi dan Kesehatan, Vol. 15, No. 1, 2026, Page 125-132
e-ISSN : 2715-9957
p-ISSN: 2354-8487

Evaluation of Papaya (*Carica papaya* L.) Seed Oil's α-Linolenic Acid and Linoleic Acid Compounds in-Silico as Antidiabetic Agents Against PPAR-γ

Kadar Ismah[1*], Yanulia Handayani[2], Claudia Dinda Safitri[3]

[1,2,3)] Pharmacy Study Program, Main Scholar Health Technology Institute, Kudus, Indonesia
e-mail:
kadarismah@gmail.com

ABSTRACT

Despite it's widespread usage in medical practice, conventional medicine is thought to cause unfavorable pharmacological reactions in the body. This is a therapy issue that is getting worse every year, particularly for people with diabetes mellitus. This study used pre-experimental computational techniques based on traditional Chinese medicine to offer a safer alternative therapy. Determining if substances in papaya seeds (*Carica papaya* L.) are effective against the PPAR-γ receptor is the goal of this study. The chemicals α-linolenic acid and linoleic acid served as test ligands in this study, while rosiglitazone was utilized as a positive control to measure binding affinity using molecular docking with Autodock Tools 4 software. By getting an RMSD value of 1,110 Å, the study's findings demonstrated that the validation procedure had satisfied the requirements. Papaya seeds (*Carica papaya* L) contain active chemicals that may have antidiabetic properties. Of these, α-linolenic acid had a stronger affinity (docking score of -6,82) than linoleic acid (docking score of -6,07). Each compound's highest score is known as the docking score. The SPSS paired T test was then used to evaluate the results. Data analysis using the paired T test reveals that there is a significant difference between the binding activity values of α-linolenic acid and linoleic acid because the p value is less than 0.05. Based on data interpretation, the binding activity values of α-linolenic acid and linoleic acid show that the data is normally distributed because the p value is >0.05..

Keywords: Herbal standardization, pharmacognostic analysis, secondary metabolites, traditional medicine, ethnopharmacology.

Introduction

Hyperglycemia, another name for diabetes mellitus, is a metabolic disease that causes blood sugar levels to rise above normal ranges(Perkeni, 2021). Damage to the pancreatic beta cells that produce insulin, which is helpful for absorbing glucose, results in hyperglycemia in people with type 1 diabetes. As a result, the body produces less ATP and the pancreatic beta cells are unable to make enough insulin (Asimina & Nebojsa, 2020). Insulin resistance is the cause of type 2 diabetes, where glucose builds up in the liver because insulin is unable to break down glucose in the

pancreatic beta cells(Agustira et al., 2019). One of the world's health risks is diabetes mellitus (DM), which can potentially be deadly and is growing annually(Madhu, 2022). This study intends to develop a healthier alternative in the treatment of diabetes mellitus by using natural chemicals that are easy to find and culture, particularly herbal plants in tropical Indonesia, in order to empower Indonesia's natural resources. Two compounds found in papaya seeds (*Carica papaya* L.) are used in this study because it is believed that both compounds can interact with the PPAR-γ receptor in a similar way, causing insulin resistance, which lowers insulin sensitivity and reduces the body's ability to produce insulin(Hardianto, 2021).

Papaya seeds from Bangkok and California have good potential as alternate sources of antioxidants and anticancer medications. Phenols, flavonoids, terpenoids, alkaloids, and fatty acids are among the discovered metabolites that combine well to show antioxidant activity and have cytotoxic effects on cancer cells in vitro. However, additional in-vivo testing is required to validate the study's finding (Alfarabi et al., 2022). Carica papaya seeds may lower blood sugar levels to control type 2 diabetes mellitus because they have demonstrated exceptional inhibitory efficacy against α-amylase and α-glucosidase enzymes as well as oxidative stress associated with diabetes. These traits, however, might be caused by bioactive substances like oleic acid, n-hexadecanoic acid, octadecanoic acid, 11-octadecenoic acid, methyl ester, pentadecanoic acid, 14 methyl, and methyl ester, which could be the cause of the effects that the Carica papaya seed extracts (Agada et al., 2020). Docking methods are widely used to identify possible ligands at the early stages of drug discovery and development. To clarify how chemicals interact with targets, a variety of programs are employed (Muhammed & Aki-yalcin, 2022). The study provides strong evidence that phytochemicals in *Carica papaya* Linn seeds have anticancer properties. Strong molecular interactions with cancer-related proteins are shown by the discovered chemicals, Dovitinib, Diphacinone, and Pyripyropene A, indicating their potential as therapeutic agents. Their potential for development into cancer therapies is further supported by their good ADMET profiles. This study supports the promise of Carica papaya as a source of novel anticancer drugs and emphasizes the importance of natural products in drug discovery (Chandra & Dakappa, 2025).

Methodology

This study uses a computer approach for quantitative pre-experimental research prior to laboratory experiments. This work employed an in silico test with Autodock Tools 1.5.6 software as a molecular docking medium. Using the Discovery Studio Visualizer 2024 Client, docking findings on ligands and proteins are prepared and visualized. The RMSD value is then obtained to assess method validity. In addition to obtaining docking scores to ascertain the affinity of the two compounds to be docked, the docking approach can be deemed genuine (correct) if the RMSD value is less than 2.00 Å. Using a positive control, the binding scores of the test compounds are compared to see if they interact with the PPAR-γ receptor to improve insulin sensitivity similarly to the positive control. If the scores from both test compounds are near the reference compound's score, the docking score is deemed good. The

difference in affinity scores between the two test compounds was then ascertained by processing the collected data using the SPSS paired T-test.

Research tools and samples

The study employed α-linolenic acid and linoleic acid, two active chemicals found in papaya seeds (Carica papaya L.), as test compounds in the binding process. The PubChem website provides samples of the active compounds found in papaya seeds (Carica papaya L.), which are then optimized using ChemDraw version 17. This study used both hardware and software as research instruments. AMD RyzenTM 3 732OU Mobile Processors with Integrated AMD RadeonTM Graphics @ 4.1 GHz max boost and 8 GB (Gigabyte) RAM (Random Access Memory) are the specifications of the ASUS Vivobook Go 14 (E1404FA RYZEN). Internet-connected laptop with AC adapter A455L ADP-65DW A. Windows 11, MGLTools version 1.5.6 with Autodock Tools version 4.2.6, Biovia Discovery Studio Visualizer 2024 Client (Accelrys Enterprise Platform), ChemOffice Professional version 17.0, and Notepad++ version 8.6.8 are among the programs utilized. In addition, the BATMAN-TCM webserver for preliminary screening is available online, as are the Protein Data Bank (PDB) and PubChem websites.

Source of Data Searching for test ligands and reference ligands on the PubChem site (http://PubChem.ncbi.nlm.nih.gov) and downloading the 2F4B receptor from the Protein Data Bank (PDB) (http://www.rcsb.org/pdb/). Ligand optimization was performed using ChemDraw version 17 software for energy minimization. Preparation of the 2F4B receptor was carried out in Discovery Studio Visualizer 2024 Client, aiming to remove water, other impurities/residues, and separate the protein chain from the native ligand of 2F4B, which is EHA201.

Preparation of ligands and proteins in Autodock Tools aims to add hydrogen atom charges and partial charges. The addition of hydrogen atom charges to the ligand can include non-polar hydrogen, and for the partial charges, Gasteiger charges can be applied. The addition of hydrogen atom charges to the protein can include polar hydrogen, and for the partial charges, Kollman charges can be applied.

Setting up the Autodock Tools (ADT) software in the Preferences menu to include a specific docking folder. Preparing the docking simulation by inputting the previously prepared ligand and receptor into ADT. Setting the grid box and docking parameters. The docking results will appear in .dlg format, which can be accessed using Notepad++. The docking results can be viewed in the Cluster Histogram table and the RMSD table. Method validation can be performed by finding the longest hashtag (#) in the Histogram column, then checking which run it corresponds to, and scrolling down to find the cluster data. After that, the RMSD value is checked; if the RMSD value is < 2.00 Å, the docking method can be continued to dock the test compound and the reference compound.

Visualization of docking results using Discovery Studio Visualizer to observe bond distances, number of hydrogen bonds, amino acids involved, compound groups involved (ligand-protein), and types of bonds formed. Binding affinity data can be processed in SPSS using the paired T-test method to determine whether there is a difference or not among the test compounds.

Research Model, and Hypothesis Formulation (if quantitative research). Also state the hypothetical relationships (hypothesis creation starts from the variables that influence the variables that are influenced)

Result and Discussion

Preparation of Ligands

The results of ligand preparation were obtained from PubChem. The two compounds were then optimized using ChemDraw software with a 3D display and output file extension (*.pdb) as shown in Figure 1. Visualization of the 3D Ligand Structure below.

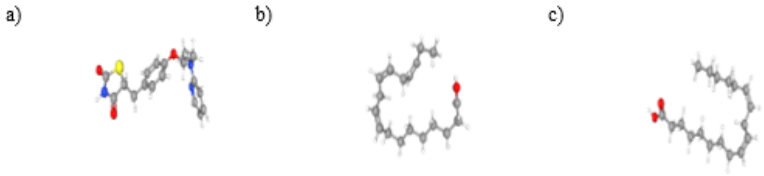

Figure 1. 3D Structure Visualization of Ligands a) rosiglitazone, b) α-linolenic acid, and c) linoleic acid

BATMAN-TCM target prediction is helpful for determining or confirming whether or not the candidate compounds can be docked. The two papaya seed compounds (Carica papaya L.) are able to bind to the PPAR-γ receptor, an insulin resistance receptor in diabetes mellitus therapy, according to the results obtained after this stage. PPAR-γ (Peroxisome Proliferator Activated Receptor-Gamma) in muscle, liver, and adipose tissue, thiazolidinediones increase the body's sensitivity to insulin and decrease insulin resistance. Additionally, gluconeogenesis is slowed down by thiazolidinediones. This class of medications includes troglitazone, rosiglitazone, and pioglitazone. Typically, biguanides (metformin) and sulfonylureas are used in tandem(Hardianto, 2021). Preparation of the 2F4B protein receptor and ligand should be done first using Discovery Studio Visualizer to remove water atoms. Water molecules present in the protein can bind with the ligand and form bonds, so it is necessary to remove the water to avoid interference during the docking process (Chen et al., 2024).

Autogrid and autodock are the two processes of calculation that are often involved in molecular docking. The autogrid setting determines the gridbox or box size, which will subsequently be the location selected to insert the ligand precisely in the middle of the box. This is done so that the ligand can travel steadily and stay in the designated orbit. After going through the technique validation stage, the grid box layout results will be used as parameters in the docking process that follows, producing the results displayed in Table 1.

Table 1. RMSD Values

Native Ligand Code	Target Protein Code	RMSD

		(Å)
E HA201 (*Rosiglitazone)*	2F4B (PPAR-γ receptor)	1,110

The flexibility of the ligand's chemical structure and the volume of the computation gridbox utilized have an impact on the final 3D structure of this ligand (Broto Santoso, 2017). RMSD and docking scores were the results of the autodock operation. Table 2 contains the RMSD value table. Because the acquired RMSD value is ≤ 2.00 Å, which shows that the synthesized ligand is similar to the original ligand, the approach can be utilized for the subsequent docking process. This implies that the method has a validity value that satisfies the RMSD requirement of 1.110 Å. Strong binding and interaction features between the ligand and receptor are indicated by a docking score that is negative and getting bigger in value (Indah Wulan Sari, Junaidin, 2020).

Table 2. Docking Score Results

Ligand	Target Protein	Docking score	active compound
Carica papaya seed	2F4B	-6,82	α-Linolenat acid
Carica papaya seed	2F4B	-6,07	Linoleat acid
Control positive (K+)	2F4B	-8,87	*Rosiglitazone* (thiazolidinediones)

The value of binding affinity, expressed in kkal/mol, represents a ligand's capacity to bind to a receptor. The affinity between the receptor and the ligand increases with decreasing binding affinity values. On the other hand, the affinity between the receptor and the ligand decreases with increasing binding affinity (Ningrat, 2022). Good binding affinity at the active site of the enzyme is indicated by a negative ΔG value, which represents the propensity for a stable ligand-receptor complex to develop. A stable binding complex is more likely to develop if the ΔG value is smaller (more negative) (Rezky Ardika pamungkas, Tiara Ajeng Listyani, 2026).

Docking scores for the α-linolenic acid and linoleic acid compounds against the 2F4B target protein were still lower than those for rosiglitazone score -8,87. The linoleic acid ligand got the highest docking score of -6.07, while the α-linolenic acid ligand had the highest score of -6.82. The binding outcomes between the reference ligand and the test ligand are observed through the visualization and analysis of docking interaction data. The visualization results show how the ligand and amino acid residues interact (Indah Wulan Sari, Junaidin, 2020). The visualization results obtained indicate that there will be a greater degree of property similarity if the binding residues are comparable to the original ligand. Both test ligands can be regarded as powerful alternative antidiabetes medicines with the target receptor 2F4B on the Peroxisome Proliferator Activated Gamma (PPAR-γ) pathway, according to the binding scores and the similarity of the involved residues. To better ensure the potency of the compounds in papaya seeds (Carica papaya L.) as antidiabetes agents, additional research can be done on absorption, distribution, metabolism, excretion

MEDFARM: Jurnal Farmasi dan Kesehatan, Vol. 15, No. 1, 2026, Page 125-132
e-ISSN : 2715-9957
p-ISSN: 2354-8487

(ADME) pharmacologically and pharmacokinetically, toxicity testing, and in vitro or in situ testing. The summary in Table 4 shows the ligand-receptor visualization results.

Table 4. Ligand and Protein Interactions

Ligand	Target Protein	The residues that bind
α-linolenat acid	2F4B	GLU343
Linoleat acid	2F4B	GLU343
Rosiglitazone	2F4B	GLU343

Ligand and Protein Interaction, visualization of the residues involved in the ligand-receptor interaction below in image 4.

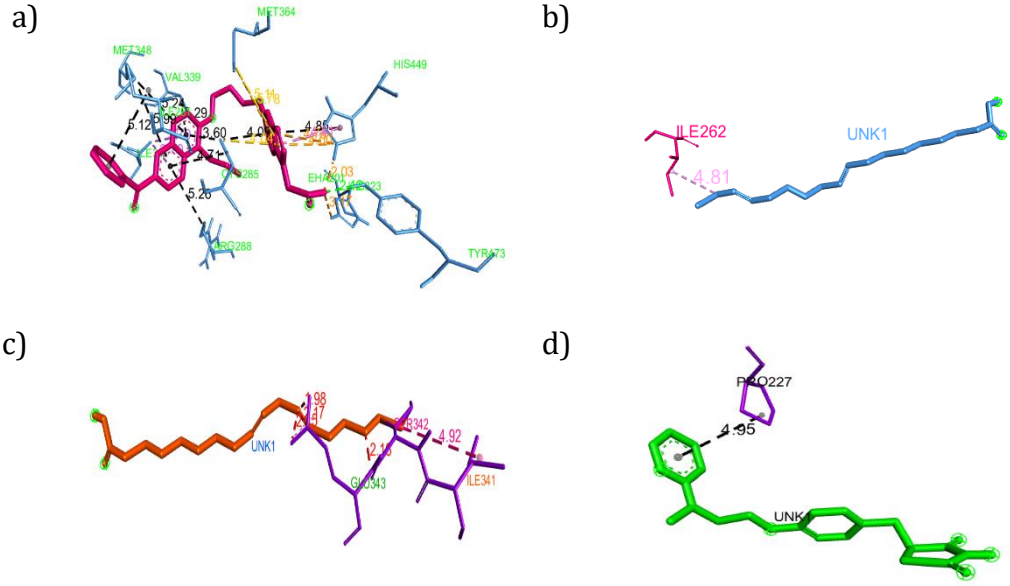

Figure 4. Visualization of Residues Involved in Ligand-Receptor Interactions a) 2F4B, b) α-linolenic acid, c) linoleic acid, and d) rosiglitazone

Following the acquisition of the docking scores, data analysis was conducted to determine the differences between cluster 1 and cluster 2 for the test compounds, using a paired t-test in SPSS. The results of the data analysis indicated that the data were normally distributed, as the p-value was > 0.05, thus allowing for data analysis using a paired t-test. The data obtained following the paired t-test indicated that there was a significant difference between the binding activity values of replication 1 and replication 2, as the p-value was < 0.05. The paired T-test method with SPSS was then used to process the obtained Δg bind value findings for the ligand. Each data set for the test compound and the positive control consisted of up to 15 samples in the histogram clustering table.

Conclusion

The active chemicals α-linolenic acid and linoleic acid found in papaya seed oil (Carica papaya L.) have been demonstrated to be potent antidiabetic medicines,

according to the research. Since α-linolenic acid has a higher binding affinity than linoleic acid, it has the highest affinity for the PPAR-γ receptor. Each test compound's maximum affinity scores were -6.82 and -6.07.

Declaration of Competing Interest

The research was carried out without any financial or commercial ties that might be seen as a potential conflict of interest, according to the author.

Reference

Agada, R., Abdullahi, W., Shehu, S., & Thagariki, D. (2020). *Heliyon In vitro and in vivo inhibitory effects of Carica papaya seed on α -amylase and α -glucosidase enzymes*. *6*(March).

Agustira, A., Darwis, I., Graharti, R., & Angraini, D. I. (2019). *Tanaman Sambung Nyawa (Gynura procumbens) sebagai Antihiperglikemi Sambung Nyawa Plants (Gynura procumbens) As Antihiperglicemic*. *9*, 240–244.

Alfarabi, M., Siagian, F. E., Cing, J. A. P. M. A. I., Suryowati, T., Suyono, M. S., & Febriyanti, M. S. (2022). *Bioactivity and metabolite profile of papaya (Carica papaya) seed extract*. *23*(9), 4589–4600. https://doi.org/10.13057/biodiv/d230926

Asimina, G., & Nebojsa, M. (2020). *Insulin Therapy in Adults with Type 1 Diabetes Mellitus : a Narrative Review*. 387–409. https://doi.org/10.1007/s13300-019-00743-7

Broto Santoso. (2017). *Pengaruh Volume Gridbox pada Docking Senyawa dalam Stelechocarpus burahol terhadap Protein Homolog antiinflamasi TRPV1*. 1–7.

Chandra, M., & Dakappa, S. S. (2025). *Molecular Docking and ADMET Profiling of Carica papaya Linn . Seed Phytochemicals : A Computational Approach to Identifying Potential Anticancer*. *3351*, 476–488.

Chen, W., He, H., Wang, J., Wang, J., & Chang, C. A. (2024). *Uncovering Water Effects in Protein–Ligand Recognition: Importance in the Second Hydration Shell and Binding Kinetics*. *25*(3), 2098–2109. https://doi.org/10.1039/d2cp04584b.Uncovering

Hardianto. (2021). *Telaah komprehensif diabetes melitus: klasifikasi, gejala, diagnosis, pencegahan, dan pengobatan*. *7*(November 2020), 304–317.

Indah Wulan Sari, Junaidin, D. P. 2020. (2020). *Studi Molecular Docking Senyawa Flavonoid Herba Kumis Kucing (Orthosiphon stamineus B.) Pada Reseptor α-Glukosidase Sebagai Antidiabetes Tipe 2*. *VII*(2), 54–60.

Madhu, S. V. (2022). *Prediction of gestational diabetes mellitus: are we ready for a biomarker lead screening strategy for GDM*

Muhammed, M. T., & Aki-yalcin, E. (2022). *Molecular Docking : Principles , Advances , and Its Applications in Drug Discovery*. 1–16.

https://doi.org/10.2174/1570180819666220922103109

Ningrat, A. W. S. (2022). *Docking Molekuler Senyawa Brazilein Herba Caesalpina Sappanis Lignum Pada Mycobacterium Tuberculosis Inha Sebagai Antituberkulosis*. *1*(1), 29–34.

Perkeni. (2021). *Pedoman Pengelolaan dan Pencegahan Diabetes Melitus Tipe 2 Dewasa di Indonesia 2021*.

Rezky Ardika pamungkas, Tiara Ajeng Listyani, T. S. W. (2026). *Analysis Of Molecular Docking Of Moringa Leaf Compounds (Moringa oleifera) On Cyclooxygenase 2 (COX 2) Enzym, Including ADME And Toxicity Prediction As An Anti Inflamatory Drug*. *11*(1).