Journal of Shifa Sciences and Clinical Research (JSSCR)
Volume 7 Number 2, 2025
Journal Homepage: http://ejurnal.ung.ac.id/index.php/jsscr, E-ISSN: 2656-9612 P-ISSN:2656-8187
DOI : https://doi.org/10.37311/jsscr.v7i2.30890

In Silico Study of *Acmella uliginosa* Leaf Compounds Interaction with Human Glucosidase

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ABSTRACT

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia due to impaired insulin secretion or action. Glucokinase (GK) plays a crucial role in glucose homeostasis and is considered a promising therapeutic target for DM treatment. This study aims to evaluate the in silico interaction between the bioactive compound N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide from Acmella uliginosa (Sw.) *and the human GK crystal structure (PDB ID: 1V4S) using Molegro Virtual Docker software. Molecular docking analysis revealed that N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide exhibits a high binding affinity to GK. Physicochemical and pharmacokinetic predictions using pkCSM indicate that this compound has a favorable pharmacokinetic profile, including high intestinal absorption and the ability to cross the blood-brain barrier. These findings suggest that N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide is a promising candidate for the development of natural product-derived antidiabetic drugs. However, further in vitro and in vivo studies are required to validate its biological activity and safety.*

Keywords:
Acmella uliginosa (Sw.)*; in silico; Molegro Virtual Docker; Glucokinase;*

Received:	***Accepted:***	***Online:***
2025-03-10	*2025-04-08*	*2025-05-01*

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disease that is a global health challenge, characterized by hyperglycemia due to impaired insulin secretion or action. One of the main therapeutic targets in DM control is the enzyme glucokinase (GK), which has a central role in the regulation of glucose homeostasis. Activation of GK is known to increase insulin secretion as well as decrease hepatic glucose production, thus making it a promising target in the development of antidiabetic agents [1],[2],[3].

In an effort to find safer and more effective antidiabetic compound candidates, exploration of natural resources, especially medicinal plants, continues to be developed. Jotang leaf (*Acmella uliginosa* (Sw.)), a plant that has long been utilized in traditional medicine, shows interesting pharmacological potential. Phytochemical studies revealed the presence of various bioactive compounds in jotang leaves, including decatrienamide derivatives, which are thought to have antidiabetic activity. However, to date, the molecular mechanism of action of these compounds on human GK is still not fully understood [4],[5].

In this context, in silico approaches become an invaluable method to explore molecular interactions between bioactive compounds and protein targets. Molecular docking, particularly using *Molegro Virtual Docker* software, allows simulation of ligand-protein interactions as well as identification of potential activation or inhibition. This

approach can provide insight into the binding affinity, interaction patterns, as well as the potential biological activity of compounds against GK [6],[7],[8].

This study aims to analyze the *in silico* interaction between bioactive compounds contained in jotang leaves (*Acmella uliginosa*), as reported in Askal Maimulyanti's study entitled *Chemical Composition, Phytochemical Screening, and Antioxidant Activity of Acmella uliginosa* (Sw.) *Cass Leaves* [9] , with the crystal structure of human glucokinase (GK) using Molegro Virtual Docker software. Through this approach, it is expected to identify potential compounds as GK activators, as well as obtain a deeper understanding of the molecular mechanism of action underlying the interaction. The results of this study are expected to make a significant contribution to the development of natural resource-based antidiabetic drugs, especially in improving the effectiveness of therapy through modulation of glucokinase as a target.

2. Methods

Hardware and Software

In this study, the hardware used is an Asus laptop with 64-bit Windows 10 operating system specifications, and an x64-based processor (AMD A4-9125 RADEON R3, 4 COMPUTE CORES 2C+2G, 2.30 GHz). The main software used for *molecular docking* simulation is Molegro Virtual Docker, which plays a role in predicting the interaction between ligand and target protein in silico to evaluate the binding affinity and stability of the complex formed.

Ligand Molecular Structure and

The main compound contained in jotang (*Acmella uliginosa* (Sw.)) leaves is N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide. For simulation purposes, the molecular structure of this compound was first drawn using ChemDraw 20.0 software, which was then converted into three-dimensional (*3D*) form using Chem3D application. In this process, the structural isomers of the main compound were retained, namely N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide.

The next step is molecular geometry optimization by utilizing the Molecular Mechanics Force Field 94 (MMFF94) method available in Chem3D. This method allows refinement of the molecular conformation by lowering its potential energy, thus obtaining a more stable and representative structure for *molecular docking* simulations.

The protein structure used as a receptor in the *docking* simulation is Crystal Structure of Human Glucokinase with Protein Data Bank (PDB) code: 1V4S, which was obtained from the Protein Data Bank (PDB) database. This protein structure was chosen because it has been experimentally characterized, so it can be used as a valid model in evaluating interactions with ligand compounds [10].

Molecular Docking Simulation

The molecular docking process was performed by evaluating the interaction between the compound N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide from jotang leaves against human glucokinase receptor protein (*Crystal Structure of Human Glucokinase*, PDB code 1V4S) using Molegro Virtual Docker software. During the *docking* process, the protein-ligand complexes were stored in Sysbil2 format, allowing further analysis of the stability of the bonds formed.

The initial stage in the simulation involves searching for *binding cavities* on the protein surface using automated detection algorithms available in the software. These cavities serve as potential sites of interaction between the protein and the ligand, which are then further analyzed to determine the binding active sites that have high affinity to the target compound.

Furthermore, the selection of the formed ligand poses is done by considering the stability and affinity of the interaction, where the ligand that has the best stability will be combined with the MMFF94 method to produce the most optimal conformation. The minimum energy of each ligand pose in the active side is evaluated using grid-based scoring method, which allows more accurate measurement of the interaction of protein molecules with ligands. The final result of this *docking* simulation is saved in Mol2 format for further analysis [7].

Docking Score Evaluation and Rating Function

Validation of the simulation results is done by evaluating various functional parameters available in the Sybil2 software. In this context, Molegro Virtual Docker uses an internal scoring function based on Dockscore, which is an algorithm that calculates the interaction value between proteins and ligands. Dockscore serves to select and distinguish the position of ligands in protein-ligand complexes, based on the calculation of ligand interaction energy and ligand internal energy. A lower score indicates a more stable interaction, so the ligand with the lowest Dockscore is selected as the candidate with the highest potential activity [11] .

Protein

The protein structure used in this study is Crystal Structure of Human Glucokinase with PDB code 1V4S. This protein is classified as a TRANSFERASE and is derived from the Homo sapiens organism, with an expression system using Escherichia coli. This protein structure does not contain mutations (*wild type*), so it can be used as a valid model in simulating ligand-protein interactions

Prediction of Physicochemical, Pharmacokinetic, and Toxicity Properties of Compounds

Prediction of physicochemical properties was carried out to characterize important parameters of the active compounds of jotang leaves related to pharmacological potential and feasibility as drug candidates. Some of the parameters analyzed include molecular weight (BM), logarithm of octanol/water partition coefficient (Log P), number of rotational bonds (torsion bonds), hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), and polar surface area (PSA). These predictions were made using the pkCMS online tool, which provides computational model-based analysis of the chemical properties of compounds.

In addition, pharmacokinetic analysis was performed to evaluate the absorption, distribution, metabolism, and excretion (ADME) of the target compound. This evaluation was done by comparing the active compound of jotang leaves with ascorbic acid and the ligand MRK_501 (A) as a comparator.

The pharmacokinetic analysis phase begins with the drawing of the compound structure in 2D format using ChemDraw, which is then converted into a 3D structure using Chem3D. Next, the molecular structure is saved in SDF (*Structure Data File*) format, which allows further conversion into SMILES (Simplified Molecular Input Line Entry System) format using the Online SMILES Translator (https://cactus.nci.nih.gov). The SMILES format is used as input in the pkCMS online tool (https://biosig.lab.uq.edu.au/pkcsm) to evaluate the pharmacokinetics and toxicity of compounds [8],[10],[12], [13].

To predict the toxicity of the compounds, the Protox II Online Tool (https://tox-new.charite.de/protox_II/) was used, which allows analysis of toxicity parameters such as LD50 (lethal dose 50%) in the Globally Harmonized System (GHS) classification system. This approach provides an estimation of the safety level of compounds when used as natural resource-based antidiabetic drug candidates. With this computational

approach, it is hoped that a comprehensive picture of the pharmacological potential, efficacy, and safety of bioactive compounds from jotang leaves will be obtained in the context of developing antidiabetic therapy based on natural compounds.

3. Results and Discussion

Molecular Structure and 3D Visualization

Structuring of the main compounds from jotang leaves was done using the ChemDraw application, as shown in Figure 1 (above). The molecular structures in 2D format were then converted to 3D using Chem3D, which allows for a more accurate representation of the molecular conformation in three-dimensional space. After conversion, the structure was saved in SYBYL2 format, which was used as input for *molecular docking* simulation (Figure 1, bottom).

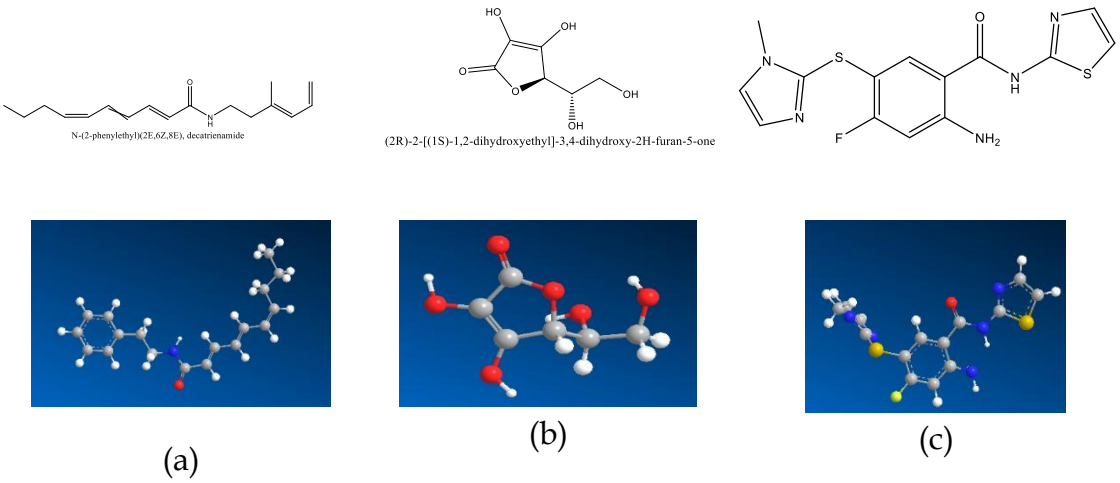
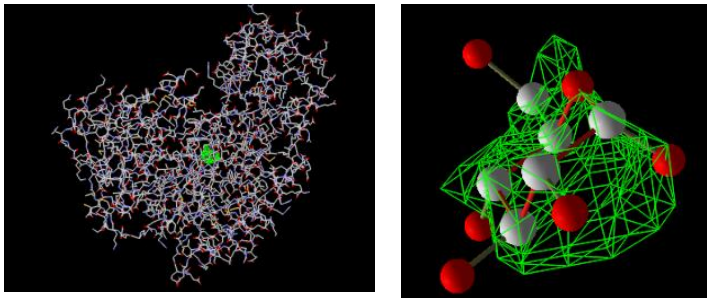


Figure 1. 2-dimensional structure of (a) jotang leaf compound; (b) ascorbic acid; (c) ligand MRK_501 (A) (top), 3D structure which is then saved in SYBTL2 format (a) jotang leaf compound; (b) ascorbic acid; (c) ligand MRK_501 (A) (bottom).

Receptor Protein Preparation and Active Site Search

The target protein structure used in this study is the Crystal Structure of Human Glucokinase with PDB code 1V4S, which was obtained from the Protein Data Bank (PDB). Once downloaded, this protein structure was then imported into the Molegro Virtual Docker software, as shown in Figure 2.

To determine the potential sites of ligand interaction with the receptor, active site (*binding cavity*) detection was performed on the protein using an automated detection algorithm. The analysis showed that cavity 4 has a volume of 25.088 $Å^3$, so it was selected as the main interaction site for the tested compounds, including the reference ligand MRK_501(A).

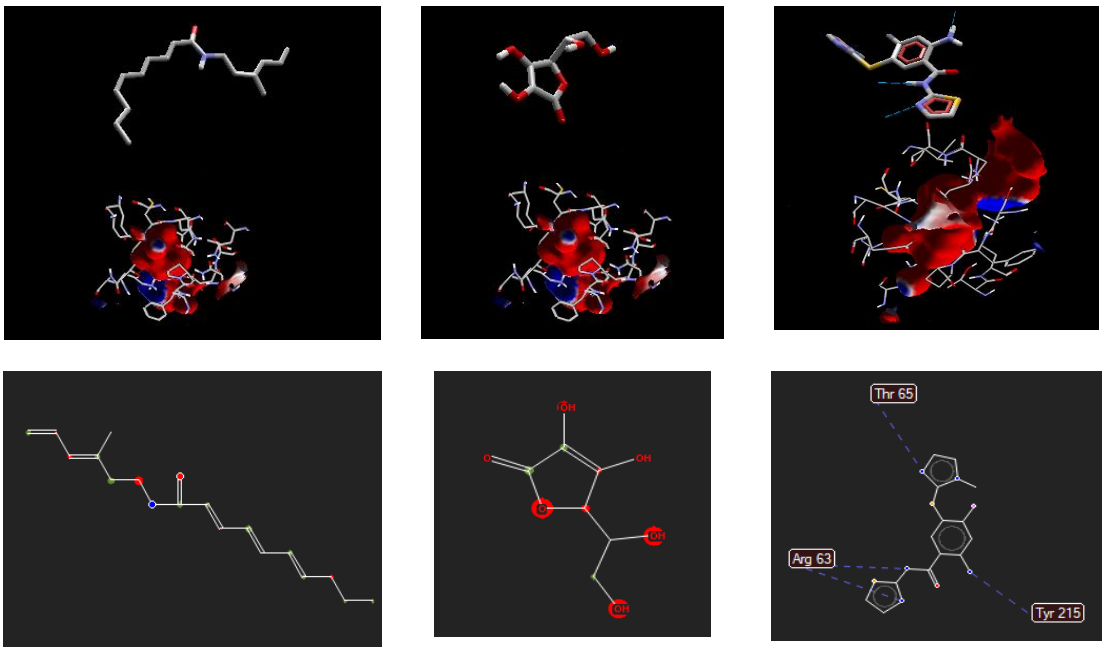


(a) (b)

Figure 2. a. Receptor Protein 1V4S; b. cavity 4 with a volume of 25.088 MRK_501 ligand (A)

Molecular Docking Analysis and Interaction with Amino Acids

A molecular docking process was performed to evaluate the binding affinity between the compound N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide and the target protein glucokinase (1V4S). The simulation results show that this compound interacts with a number of amino acid residues in the active site of the protein, as shown in Figure 3.



(a) (b) (c)

Figure 3. List of Amino Acids involved in docking interactions with jotang Leaf compounds (a), Ascorbic Acid (b), MRK_501(A) ligands (c)

Further analysis results are shown in Table 1, which contains the *re-docking* scores of each compound. Based on the Rerank Score values, N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide and MRK_501(A) showed better binding affinity compared to ascorbic acid, which had a higher score and indicated a weaker possible interaction. From these data, it can be concluded that the compound N-(2-phenylethyl)(2E,6Z,8E)-

decatrienamide has potential as a glucokinase activator, with a docking score value close to the reference ligand MRK_501(A).

Table 1. Re-Docking results using Molegro Virtual Docker application

Re Docking	*N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide*	Ascorbic Acid	MRK_501(A)
I	-105.915	-79,632	-105,373
II	-100,078	-73,627	-103,791

Prediction of Physicochemical and Pharmacokinetic Properties

Prediction of physicochemical properties was performed using the pkCMS online tool, which includes evaluation of molecular weight (BM), octanol-water partition coefficient (Log P), number of rotational bonds (torsion), number of hydrogen bond donors and acceptors (HBD, HBA), and polar surface area (PSA). The prediction results are shown in Table 2.

Table 2: In silico prediction results and physicochemical properties of jotang leaf, ascorbic acid, MRK_501 ligand (A)**.**

Parameters	*N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide*	Ascorbic Acid	MRK_501(A)
BM	259.393	176.124	349.416
Log P	4.0937	-1.4074	3.0014
Torsion	9	2	4
HBA	1	6	7
HBD	1	4	2
PSA (A2)	116.842	67.321	139.114

The data provided compares three compounds based on important chemical and pharmacological parameters. Molecular weight (BM) indicates the size of the molecule. From the data, it can be seen that MRK_501(A) has the largest molecular weight (349,416), followed by N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide (259,393), and Ascorbic Acid (176,124). This indicates that MRK_501(A) is the largest molecule among the three [7]. The octanol-water partition coefficient (Log P) measures lipophilicity or hydrophobicity. N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide has a high Log P (4.0937), indicating strong lipophilic properties. In contrast, Ascorbic Acid has a negative Log P (-1.4074), indicating strong hydrophilic properties. MRK_501(A) is also lipophilic with a Log P of 3.0014, although not as strong as the first compound.

The number of rotatable bonds (Torsion) reflects the flexibility of the molecule. N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide has the highest flexibility with 9 rotatable bonds, followed by MRK_501(A) with 4, and Ascorbic Acid with 2. In addition, the number of hydrogen bond acceptors (HBA) and hydrogen bond donors (HBD) indicates the ability of hydrogen bond formation. Ascorbic Acid and MRK_501(A) have greater hydrogen bond accepting ability, while Ascorbic Acid has the highest hydrogen bond donating ability [14] . Polar surface area (PSA) correlates with cell membrane penetration ability. MRK_501(A) has the highest PSA (139,114 $Å^2$), followed by N-(2-

phenylethyl)(2E,6Z,8E)-decatrienamide (116,842 Å²), and Ascorbic Acid (67,321 Å²). The high PSA value of MRK_501(A) indicates a greater potential for polar interactions with the biological environment.

Based on these data, the compound N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide showed high lipophilic properties (Log P = 4.0937), indicating the possibility of good membrane permeability. However, the polar surface area (PSA = 116.842 Å²) is still within the range that allows for good oral absorption.

Table 3. In silico prediction of pharmacokinetics and toxicity of Jotang leaf, Ascorbic acid, MRK_501 ligand (A)

ADMET	*N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide*	Ascorbic Acid	MRK_501(A)
Intential absorption (human)%	92.346	39.716	90.448
Skin Permeability (Log P)	-2.058	-3.478	-2.735
VDss (human) (Log L/kg)	0.245	-0.264	0.07
BBB Permeability (Log BB)	0.678	-1.233	-1.227
CYP2D6 Substarte (Yes/No)	No.	No.	No.
CYP2D6 inhibitor (Yes/No)	No.	No.	Yes
Total Clearence (Log ml/min/kg)	0.768	0.623	0.744
Renal OCT substrate (Yes/No)	No.	No.	Yes

In addition to the physicochemical properties, pharmacokinetic evaluation was also conducted using pkCMS to identify ADMET (Absorption, Distribution, Metabolism, and Excretion) parameters. The data obtained are summarized in **Table 3**. Table 3 provides important information on the pharmacokinetic properties of the three compounds, which are highly relevant in drug development: Intestinal Absorption (Human): This parameter measures the percentage of the compound absorbed in the human gut. N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide and MRK_501(A) showed high absorption (92.346% and 90.448%), indicating good absorption in the gut. Ascorbic acid had a lower absorption (39.716%), probably due to its hydrophilic nature. Skin Permeability (Log P): A negative value indicates the compound is difficult to penetrate the skin. All three compounds had negative values, with Ascorbic Acid showing the lowest skin permeability (-3.478), followed by MRK_501(A) (-2.735), and N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide (-2.058). Volume of Distribution (VDss) (Human): VDss indicates the distribution of the compound throughout the body. N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide had the highest VDss (0.245 Log L/kg), followed by MRK_501(A) (0.07 Log L/kg), and Ascorbic Acid (-0.264 Log L/kg). Brain

Blood Barrier (BBB) Permeability (Log BB): Log BB measures the ability of compounds to penetrate the blood brain barrier. N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide had a positive value (0.678), indicating it can penetrate the blood brain barrier, while Ascorbic Acid (-1.233) and MRK_501(A) (-1.227) had negative values, indicating they are difficult to penetrate the blood brain barrier. CYP2D6 Substrates and CYP2D6 Inhibitors: CYP2D6 is an enzyme involved in drug metabolism. All three compounds are not CYP2D6 substrates. MRK_501(A) is a CYP2D6 inhibitor, which means it may inhibit the metabolism of other drugs metabolized by this enzyme. Total Clearance (Log ml/min/kg): Clearance measures the rate at which a compound is eliminated from the body. All three compounds had relatively similar clearances. Renal OCT Substrate: MRK_501(A) is a Renal OCT substrate, which means this compound interacts with Renal OCT, where Renal OCT is a transporter protein present in the kidney [1], [2],[15] .

Although the results of this study indicate that N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide has potential as a glucokinase activator, there are several limitations that need to be considered. This study only used an in silico approach, so experimental validation with in vitro and in vivo tests is still needed to confirm the *molecular docking* results and pharmacokinetic predictions obtained. In addition, this study did not include molecular dynamics simulations, which could have provided a deeper understanding of the stability of ligand-protein complexes in a more realistic biological environment. Although the interactions between the test compounds and glucokinase have been analyzed, the potential effects of these compounds on other metabolic pathways, as well as possible long-term toxicity, have not been further explored. Therefore, further studies that include experimental validation are urgently needed to confirm the effectiveness and safety of these compounds as antidiabetic drug candidates.

4. Conclusion

The results of this study showed that N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide, a major compound in jotang (*Acmella uliginosa*) leaves, has potential as a ligand for human glucokinase (GK) protein based on *molecular docking* results that showed high binding affinity and strong interaction with GK. Pharmacokinetic predictions showed that this compound has high intestinal absorption as well as the ability to cross the blood brain barrier (BBB), which supports its potential in biological systems. However, this study is still limited to the in silico approach, so experimental validation with in vitro and in vivo tests is needed to confirm the *molecular docking* results and evaluate the pharmacological effectiveness and safety of this compound more thoroughly. In addition, molecular dynamics simulations can be performed to understand the stability of ligand-protein complexes in a more realistic biological environment. Further tests on acute and chronic toxicity, as well as potential side effects, are also needed to determine the safety of this compound before further development as an antidiabetic drug candidate. In addition, structural optimization of the compound through chemical modification can be considered to improve the pharmacokinetic and pharmacodynamic potential, as well as reduce the possibility of unwanted side effects. With further research that includes experimental validation and further evaluation, it is expected that N-(2-phenylethyl)(2E,6Z,8E)-decatrienamide can be developed as a more effective and safe natural resource-based antidiabetic therapeutic agent candidate.

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