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Research Article

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In silico Approaches to Identify Phthalic Acid Derivatives as Inhibitors Tyrosinase, α-Glucosidase, and Dipeptidyl peptidase-4

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Abstract

Integrating scientific and technological development in medicinal chemistry implies a great leap forward and speeds up the low-cost drug discovery process from natural resources. Therefore, in silico approaches were performed through molecular docking involving receptors crucial in metabolic processes, aiming to gain insights into how free radicals bind and how blood sugar levels can be lowered. The research aims to study the inhibitory mechanisms of phthalic acid derivatives such as tyrosine enzymes, alpha-glucosidase, and dipeptidyl peptidase-4 with in silico predictions. The in silico prediction instrument is in the form of computing software. Additional ligand sources were gained from a database of tyrosinase enzyme receptor (6JU9), alpha-glucosidase receptor (2JKE), and dipeptidyl peptidase-4 (1N1M). The active ingredients of Kenikir and Yacon leaves are used as test compounds with comparison drugs such as acarbose. The *Diisooctyl Phthalate* compound has an antioxidant potential through the 6JU9 target protein, with the most stable docking score of -81, 07. The target proteins for reducing blood sugar levels each have a value of -61.606 (2JKE ligand) and -86.945 (1N1M ligand). It is concluded that natural resources (*Cosmos caudatus* and *Smallanthus sonchifolius*) showed potential as natural drugs with an in silico approach study.

Keywords: Diisooctyl phthalate; Phthalic acid; di (2-propylpentyl) ester; Bioinformatics; Docking.

1. Introduction

In-silico methods have emerged as a crucial element in discovering drugs, involving creating and identifying potential drug candidates through computer-based techniques using pharmacophore models [1]. Computational techniques aid in the creation of new drug candidates (ligands) that exhibit improved bioactivity [2]. Molecular docking serves as a computational chemistry approach to ascertain the anticipated interactions between a receptor molecule and ligand, thus predicting the conformation of the ligand and the effective binding site activity of a substance [3].

People in Indonesia tend to prefer traditional medicinal plants over synthetic medications, believing they lead to fewer adverse effects and are more readily available. Various plants have been recognized for their potential as traditional herbal remedies to address different ailments, such as the knicker plant (Cosmos

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Caudatus) and the yacon plant (Smallanthus sonchifolius). Kenikir leaves exhibit notable antioxidant properties [4]. Research has indicated that this plant may help diminish the risks of heart disease, stroke, arthritis, inflammation, and cancer [5]. On the other hand, yacon leaves are beneficial in treating diabetes, as yacon leaf extract contains secondary metabolites that are instrumental in the glucose metabolism process [6].

Diabetes mellitus ranks as the fifth leading cause of death globally, following sepsis, stroke, liver disease, and tuberculosis [7]. In 2014, approximately 422 million individuals worldwide were affected by diabetes mellitus, and this number has increased fourfold since 1980. The World Health Organization (WHO) projects that the prevalence of diabetes mellitus, particularly type 2 diabetes, will continue to rise [8]. Utilizing in-silico methods is typically more economical and straightforward since it eliminates the need for laboratory tools and live animal experimentation [9].

Diabetes mellitus has a high prevalence in the world, and the incidence has increased over time. Diabetes mellitus is caused by increasing blood sugar levels, causing increasing insulin production. Acarbose is a class of alpha-glucosidase enzyme inhibitor drugs commonly used to prevent postprandial hyperglycemia [10]. The alpha-glucosidase enzyme is an enzyme that can break down carbohydrates into monosaccharide compounds, which will be absorbed using a certain transport mechanism. Inhibition of the alpha-glucosidase enzyme will reduce monosaccharide absorption into the blood, thereby preventing postprandial hyperglycemia [11]. Apart from the alpha-glucosidase enzyme, the dipeptidyl peptidase 4 (DPP4) enzyme controls glucose metabolism. The dipeptidyl peptidase four enzymes can degrade incretin or Glucagon-like peptide 1 (GLP-1) [12]. Incretin plays a role in controlling blood glucose levels by increasing insulin secretion. Inhibition of the DPP4 enzyme will increase insulin secretion in regulating blood glucose levels [13].

Leveraging insights on the binding affinity of molecules to their target active sites represents an advanced strategy within drug design. Furthermore, research by Ahkam et al. (2020) indicates that molecular docking analyses revealed that gingerenone, a compound present in red ginger, demonstrated the lowest binding energy when interacting with the S protein and Mpro compared to other compounds found in red ginger. Consequently, red ginger is believed to have the potential to inhibit the SARS-CoV-2 virus, which infects human host cells and could be developed into an effective medication with good bioavailability.

A notable number of studies concentrate on various approaches based on ligands and structures, or a blend of both, to find potential molecules for specific targets. Integrated method that combines structure and ligand data to explore the structural factors that affect the binding affinity of several compounds to the human Sigma1 receptor (S1R) [14]. This receptor is considered a significant target for developing treatments for neuropsychological conditions. The researchers identified a strong S1R agonist named RC-33, which shows promise as a neuroprotective agent. In an article on this Research Topic, the authors used computational methods to analyze how RC-33 and its new derivatives interact with the active site of S1R. They applied various computational techniques to examine the ligand-protein interactions. The findings revealed that employing a mix of different in silico methods can enhance the drug discovery process [15].

This research intended to predict and modify compounds derived from Phthalic Acid Esters to inhibit the activity of enzymes such as tyrosinase, alpha-glucosidase, and dipeptidyl peptidase-4. The in silico predictions suggest these compounds could serve as potential agents for antioxidant and antidiabetic treatments. It is anticipated that this study will benefit healthcare professionals, allowing the use of yacon leaves and knicker leaves as alternative herbal remedies for diabetes and oxidation while also providing references to chemical compounds capable of inhibiting DPP-4 enzyme activity from preventing elevated blood sugar. This includes focusing on the enzymes tyrosinase, α-glucosidase, and dipeptidyl peptidase- 4, contributing valuable information for future research efforts.

2. Materials and Methods

This research was conducted using molecular docking techniques with three enzyme receptors: the tyrosinase enzyme (code 6JU9), the alpha-glucosidase receptor (code 2JKE), and dipeptidyl peptidase-4 (code 1N1M). The active compounds from Keniker and Yacon leaves were tested against comparison drugs, such as acarbose.

The in silico prediction was performed using various computational software tools, including Protein-Ligand ANTSystem (PLANTS), Yet Another Scientific Artificial Reality Application (YASARA), Prediction of Activity Spectra for Substances (PASSOnline), and the Search Tool for the Retrieval of Interacting Genes/Proteins Database (string.db).

2.1. Ligand preparation

The structure of the ligand target was determined based on the most dominant compound identified through Gas Chromatography-Mass Spectrometry (GC-MS) separation. The chemical compounds obtained exhibit antioxidant and antidiabetic potential. Using the Simplified Molecular Input Line Entry System (SMILES), we conducted a Prediction of Activity Spectra for Substances (PASS) analysis to evaluate the biological activity spectrum of the knicker and yacon leaf isolate fractions. This process is facilitated through a bioinformatics approach, and the results are presented accordingly.

2.2. Preparation Protein Structures

The protein sequence was obtained from the Research Collaboratory for Structural Bioinformatics (RCSB) website and downloaded from the 6JU9, 2JKE, and 1N1M databases. The Researcher used the PASS and STRING databases to predict and analyze protein interactions. Protein macromolecule receptors were separated from other molecules and their ligands using the YASARA application. Protein validation was performed with the YASARA software, achieving an RMSD value of less than 2 Årmströng. The results are saved in .mol2 format, named after the protein.

2.3. Validation of the Docking Method

PLANTS validates the docking tool for docking score. The more negative docking scores describe the compound's effectiveness or potential as an antioxidant and antidiabetic. LigPlot and Pymol were used to study protein-ligand interactions, such as the residues involved and their interactions, which are then compared with the original ligand.

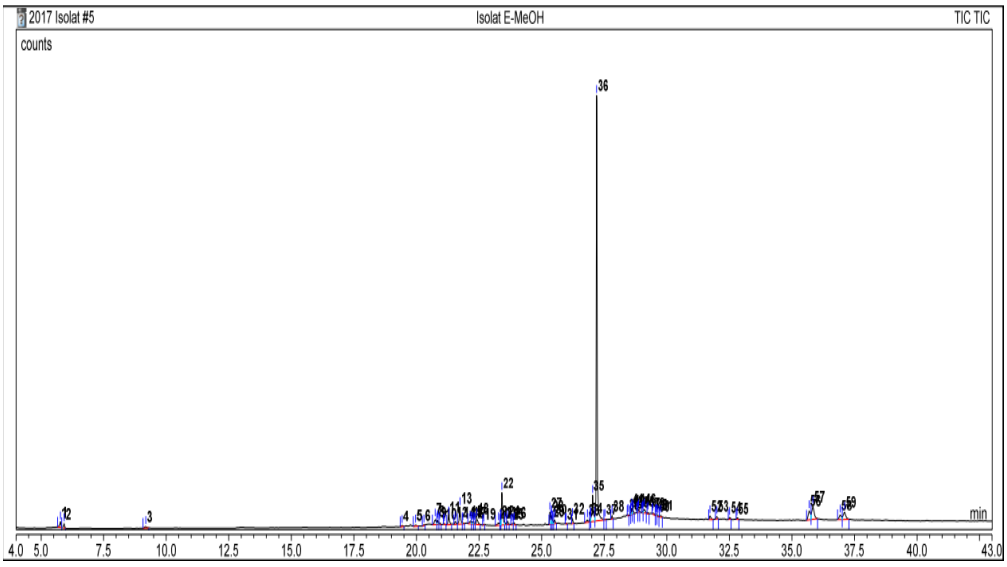
3. Results and Discussion

Kenikir leaves are a tropical herbal plant with abundant antioxidants, widely used to treat various disease disorders [4]. Like other tropical plants, yacon leaves also show the effect of being able to lower blood sugar levels because they have a secondary metabolite that plays many roles in the glucose metabolism process, such as enhydrin [6].

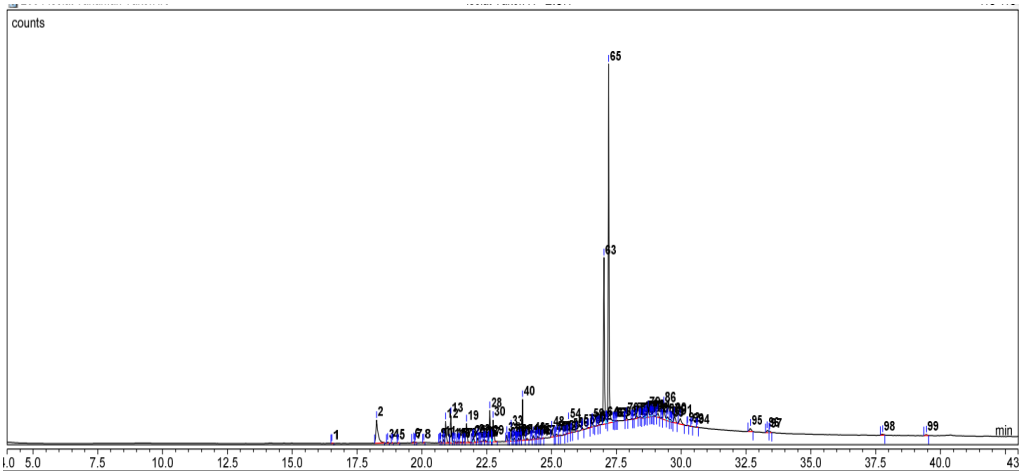
A previous study reported that kenikir leaves (*Cosmos caudatus*) have antioxidant activity because they contain phenolic and flavonoid compounds [16]. A recent study reported that quercetin and its derivate compounds were found in the isolation of knicker leaves. Other studies show the content of phenolic compounds such as gallic acid, caffeic acid, chlorogenic acid, and coumaric acid. Phenolic compounds and flavonoids are known to have good antioxidant activity in preventing exposure to free radicals [17]. Meanwhile, isolated compounds found in yacon leaves are **smallanthaditerpenic** acid and **nyctose**. These two compounds inhibit the alpha-glucosidase enzyme in controlling blood sugar levels [18]. The differences in results that appeared could be caused by differences in the conditions and separation methods used, which influenced the obtained isolates.

Exploring the potential compound content of knickers and yacon leaves is an opportunity to develop herbal medicines as an alternative for preventing free radicals or antioxidants and treating diabetes. Utilization of computational or in silico methods is helping us to identify and make predictions of the biological activity of a molecule that has the potential to be developed into a drug [19].

Three ligands from the active ingredients of kenikir and yakon leaves are used in this research. Based on the results of GC-MS chromatography, knicker leaves contain Diisooctyl phthalate (DIOP) compounds, and this is proven by the GC-MS spectrogram showing that the DIOP compound has the most dominant peak with a retention time of 27.20 with an area of 42.04%, as in the figure (**figure 1**). The DIOP compound is included in the derivative of the phthalic acid ester (PAE) compound. Yakon leaves have also been shown to contain derivatives of the PAE compound, Phthalic acid, di(2-propylpentyl) ester. The results of the GC-MS chromatography analysis showed that one most dominant peak appeared in the fraction, Phthalic acid compound, di(2-propylpentyl) ester. This compound is thought to be the most dominant in isolate H, so this compound can be tethered to an enzyme that plays a role in blood glucose metabolism (alpha-glucosidase) to see the potential for antidiabetic activity.



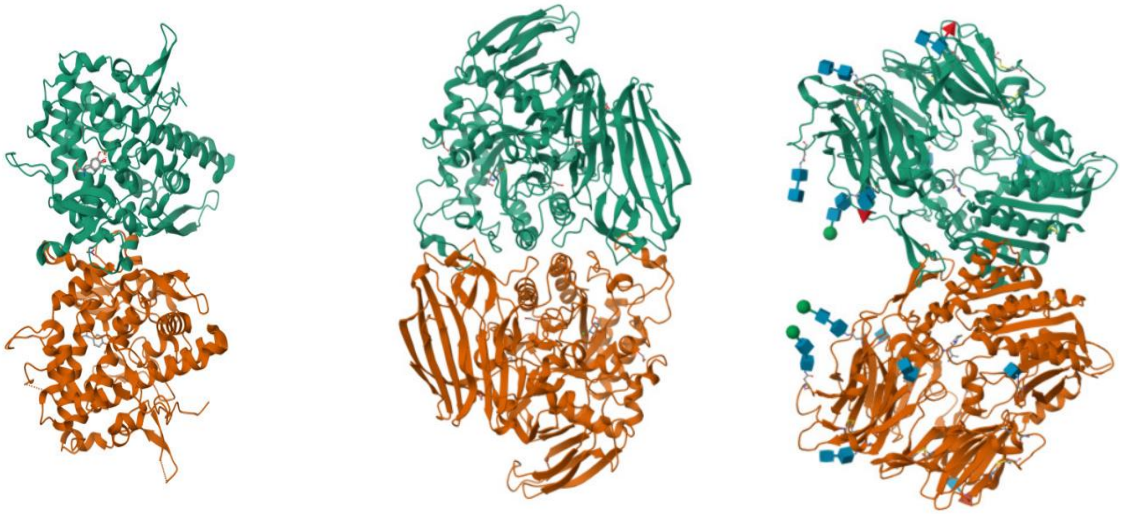
(a)



(b)

Figure 1. (a) GC-MS spectrum of isolated compounds from knicker leaves (b) GC-MS spectrum of isolated compounds from yacon leaves.

Molecular docking predicts the activity of a chemical molecule by observing the interactions between its molecular structure and the target ligand [20]. The selection of target receptors is based on enzymatic reactions. In this context, tyrosinase was a valuable target for preventing neurodegeneration and addressing hyperpigmentation issues. This is because tyrosinase's mycophenolate activity catalyzes tyrosine intermediates' conversion to L-DOPA, a critical and rate-limiting step in melanin synthesis. Discovering new enzyme inhibitors is of great interest in the fight against degenerative diseases. There is a pressing need for multifunctional compounds that can simultaneously modulate multiple interconnected pathological pathways. The antioxidant potential associated with the tyrosinase enzyme and antidiabetic effects observed through inhibiting alpha-glucosidase and dipeptidyl peptidase-4 enzymes support this approach. The tyrosinase receptor was obtained from the Protein Data Bank (PDB) with the code 6JU9 (**Figure 2.a**) for further validation. The receptor for alpha-glucosidase was also sourced from the PDB, identified by the code 2JKE (**Figure 2.b**), and for dipeptidyl peptidase-4, the code is 1N1M (**Figure 2.c**).



(a) (b) (c)

Figure 2. ID PDB (a) 6JU9, (b) 2JKE, dan (c) 1N1M

3.1. Docking Validation

Validation of target proteins to find binding sites to use as a reference for molecular docking. Docking validation uses the active site of the 6JU9, 2JKE, and 1N1M receptors as ligand docking sites to inhibit enzyme activity. The 6JU9 receptor has native ligands, ref_ligand, gallic acid, quercetin, and kojic acid, while 2JKE binds to the native ligand 1-deoxynojirimycin and 1N1M to the native ligand valine. Docking validation on native proteins and ligands, with a Root Square Mean Deviation (RMSD) value of no more than 2 Armstrong (Å), because a smaller RMSD value indicates that the ligand position is estimated to be better because it is closer to the native conformation [21].

The results of the RMSD value during the validation process between the native ligand and the 6JU9 receptor were obtained at 0.416 Å, while from the 2JKE receptor, it was 0.2976 Å and 1N1M was 1.1548 Å. Based on literature studies, a target protein is declared valid if it has a range of RMSD values <Å; therefore, it is valid and can be used as a target protein for molecular docking [22].

3.2. Molecular Docking

The docking score indicates a measure of a drug's ability to bind to a receptor, where the smaller the docking score, the higher the affinity between the receptor and the ligand, but the larger the docking score, the lower the affinity between the receptor and the ligand [21].

The docking process on the 6JU9 receptor involves 10 conformer forms of compounds identified by GC-MS as ligands with macrospecies value criteria (pH) of 7.4. For the 10 conformer forms, the diisooctyl phthalate compound has the largest average of -81.070 with a standard deviation of 4.064 compared to 3 comparison compounds of gallic acid, quercetin, and kojic acid, indicating that the correlation between the docking score and the energy arising from the drug complex with the receptor will be more stable [23]. The comparison compounds each has values of -68.020 (quercetin), -60.032 (gallic acid), and -57.684 (kojic acid), indicating that the energy of the drug receptor complex is more unstable because the docking score value is high compared to the diisooctyl phthalate compound.

A previous study reported that the isolated compound obtained from the ethanol extract of yacon leaves was **nyctose** as an alpha-glucosidase enzyme inhibitor [24]. Alpha-glucosidase enzyme inhibitory activity was proven through an in silico approach with molecular docking and in vitro test [25]. Other research reported that **nyctose** also shows inhibitory activity against the DPP4 enzyme when tested using molecular docking [24]. Quercetin compound has been reported to be found in kenikir leaf extract. Quercetin has good antioxidant

activity. A previous study showed that quercetin interacts well with the tyrosine kinase enzyme, as proven by a good docking score [26].

As a ligand, the 2JKE receptor is anchored with a phthalic acid molecule, di(2-propylpentyl) ester. The docking score of the ligand molecule will be compared with the native PDB ligand, the 1-deoxynojirimycin molecule, an alpha-glucosidase enzyme inhibitor molecule. The docking results of the phthalic acid molecule, di(2-propylpentyl) ester, are not good at -61.606 compared to the average comparative docking value of -77.124. This difference indicates that phthalic acid, di(2-propylpentyl) ester tends to be less potent than the 1-deoxynojirimycin compound as an alpha-glucosidase enzyme inhibitor so that the potential of the compound as an antidiabetic is lower [9]. The smaller the docking value, the more stable the interaction between the ligand and the receptor will be so that its inhibitory activity will improve [22].

The docking between the 1N1M receptor and the phthalic acid ligand, di(2-propylpentyl) ester, will be compared for its docking score with the valine comparator, which is a molecule that inhibits the enzyme dipeptidyl peptidase-4. This enzyme influences glucose metabolism and its ability to degrade Glucagon-like-peptide 1 (GLP-1). Inhibition of this enzyme will increase the activity of GLP-1, which will stimulate insulin production so that it can lower blood sugar levels [27]. The docking results showed a significant difference between the phthalic acid compound di(2-propylpentyl) ester, which obtained a docking score of -86.945, while the comparator was -75.048. These results indicate that phthalic acid, di(2-propylpentyl) ester, has better potential than valine as an inhibitor of the enzyme dipeptidyl peptidase-4.

3.3. Visualization of docking results

The docking results are visualized to determine the interaction between the receptor's ligand and amino acid residues [21]. Interactions that occur are hydrogen bonds or hydrophobic interactions. Hydrogen bonds can be formed due to the interaction between hydrogen atoms and electronegative compounds such as oxygen, fluorine, and nitrogen [19].

Diisooctyl phthalate compound interacts with tyrosinase receptor (6JU9) as many as 15 amino acid residues; it can be predicted that this interaction is the best compared to the comparison compounds gallic acid, quercetin, and kojic acid. **Figure 3** shows the visualization of 2D docking results against amino acid bonds.

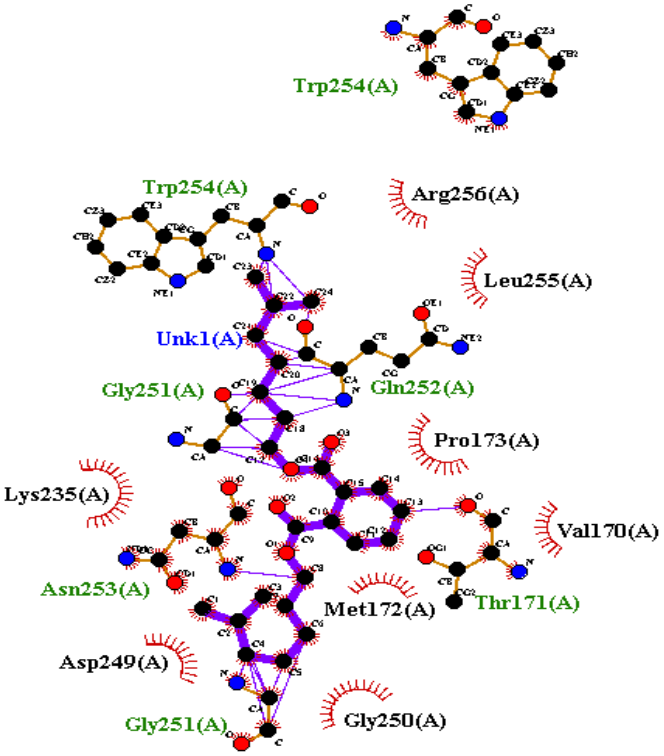


Figure 3. Visualization of the 2D docking results of diisooctyl phthalate (DIOP)_6JU9 against amino acid bonds.

Diisooctyl phthalate compound has a ligand-shaped bond with the drug receptor and has more amino acids than the standard quercetin and the original ligand of the 6JU9 receptor (**Table 1**). The absence of hydrogen bonds is formed, indicating the potential for modification of the compound to increase potency. DIOP_6JUP has interactions with 15 different amino acids. The Kojic Acid_6JUP compound binds 2 glutamine amino acids (3.08 Å) and 2 tryptophan (2.99 Å) in the target protein, while the original ligand binds 2 asparagine and 2 glutamine, respectively.

Amino acids of type Gln252, Trp 254, and Asn253 bind to the target 6JU9 receptor induced by the isolated compound DIOP, the quercetin comparison, and the original ligand. This indicates the same location for the ligand and receptor linkage. However, as a differentiator, the isolated compound (DIOP) binds the same three types of amino acids. Also, it interacts with 12 other different amino acids, increasing the compound's stability as a drug target.

Diisooctyl phthalate compound is marked in red, and amino acids are marked in yellow (**Figure 4**). Diisooctyl phthalate compound (absence hydrogen bond) is formed, but rather the receptor-ligand and hydrophobic interaction. This indicates a less stable bond and is not recommended as a new drug design.

Table 1. Tabulation of amino acid binding in docking compounds

Compound	Amino Acid Amount	Amino Acid Type	Bond	Long
DIOP_6JU9	7 amino acid	Trp254 (A); Gln252 (A); Gly251 (A); Thr 171 (A); Asn253 (A)	Ligand Binding	-
	8 amino acid	Gly250 (A); Asp249 (A); Lys235 (A); Met172 (A); Val170 (A); Pro173 (A); Leu255 (A); Arg256 (A)	Hydrophobic	-
Kojid Acid_6JU9	2 amino acid	Gln252 (A); Trp254 (A): Gln252 (A); Trp254 (A)	Ligand Binding	3,08 Å 2,99 Å
	3 amino acid	Gly251(A); Asn253 (A)	Hydrophobic	-
refLigand_6JU9	4 amino acid	Asn253 (A); Gln252 (A); Gln252 (A); Asn253 (A)	Ikatan Ligan	-
	2 amino acid	Gly251 (A); Trp254 (A);	Hydrophobic	-

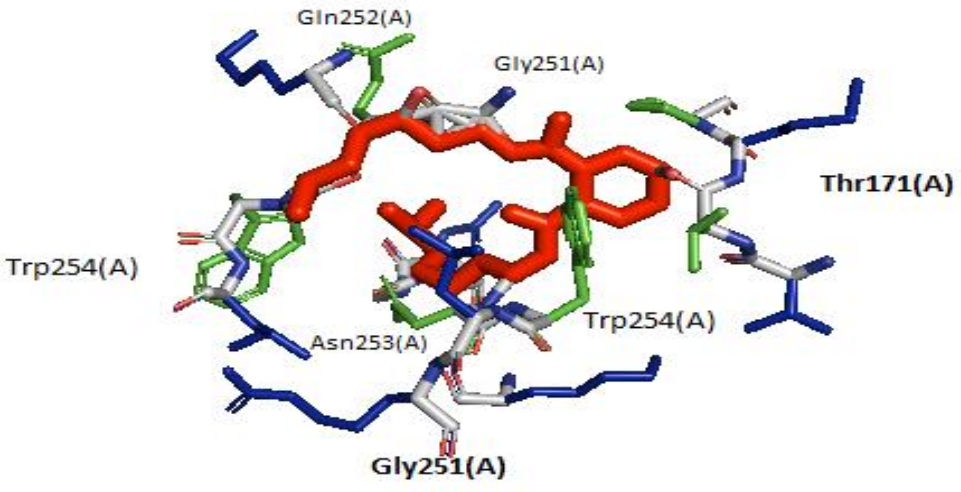


Figure 4. Visualization of the 3D docking results of diisooctyl phthalate (DIOP)_6JU9 against amino acid bonds.

The docking visualization results using Pymol, 3D visualization shows color with meaning, and red shows the isolated compound diisooctyl phthalate, green marks direct amino acid interaction with the compound, blue represents indirect amino acid interaction, and white indicates the presence of hydrogen bond. The hydrogen bond is between an H atom with a positive charge and other electronegative atoms such as O, N, and F. In addition to interactions through hydrogen bonds, other interactions with amino acid residues are also seen. The more interactions between the compound diisooctyl phthalate with amino acid residues, the better the interaction is predicted [28].

The visualization results of phthalic acid molecules, di(2-propylpentyl) ester with alpha-glucosidase enzyme are shown in **Figure 5**. The figure shows the presence of hydrogen bonds with amino acid Trp485 and hydrophobic bonds with amino acids Arg449, Val444, Asn446, Ser443, Tyr447, Arg477, and Asp406. Meanwhile, the original ligand (1-deoxynojirimycin) has a hydrophobic interaction with amino acids Val444, Glu448, Arg445, and Pro476. Phthalic acid, di(2-propylpentyl) ester, and 1-deoxynojirimycin compounds with the lowest docking scores both interact with Val444 and Trp485 which are likely the active sites of the alpha-glucosidase enzyme [29].

The difference in the amount of amino acid interacting with the ligand will affect the results of the obtained binding energy and docking score. The binding energy of the phthalic acid molecule, di(2-propylpentyl) ester, is greater than the original ligand 1-deoxynojirimycin due to the difference in the amino acids that bind, thus affecting the binding energy and affinity [29].

The research compared the compound's original ligand with the drug molecule acarbose. Acarbose is a type of antidiabetic drug in the alpha-glucosidase enzyme inhibitor group and has been widely used to control blood sugar levels in diabetic patients. **Table 2** presents comparative data between the test molecule, the original ligand, and the acarbose drug. This test aims to observe how acarbose interacts with the alpha-glucosidase receptor. From this comparison, the acarbose drug compound has a docking score that tends to be high; therefore, the compound is more unstable than the test molecule.

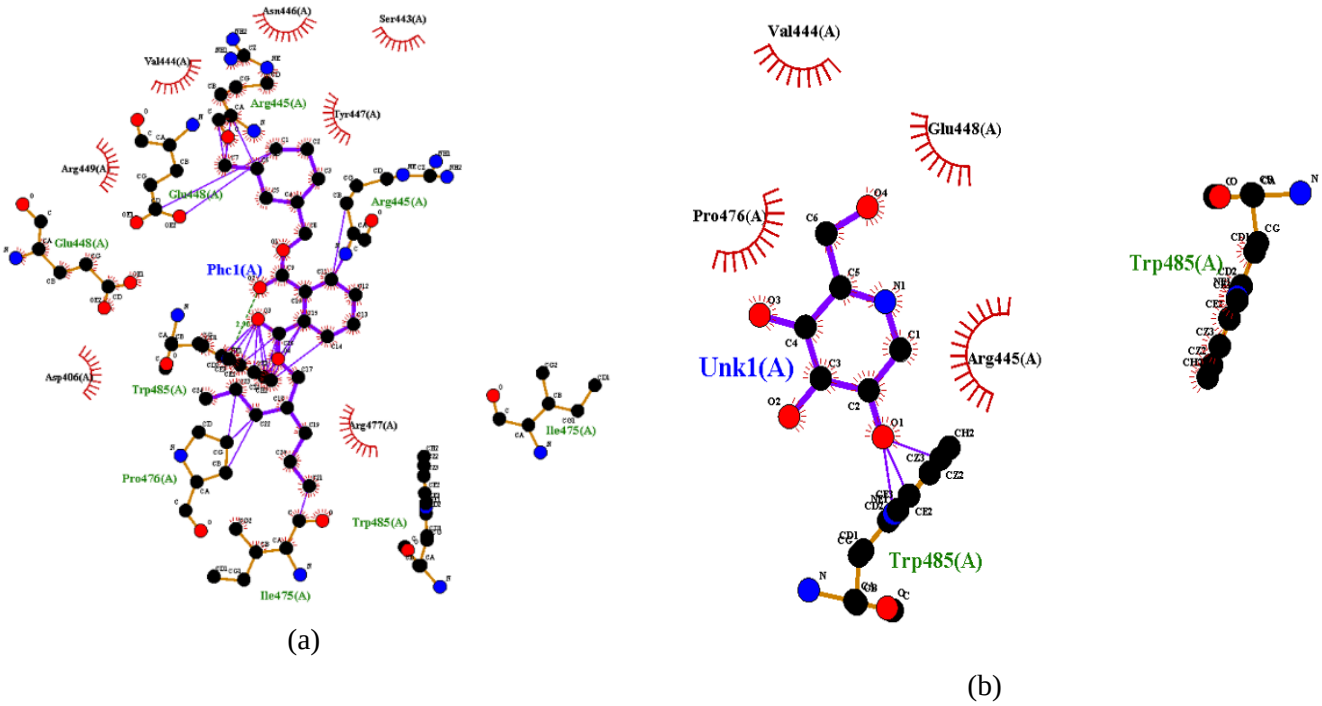


Figure 5. 2D visualization of the docking results of the 2JKE receptor (a) phthalic acid, di(2-propylpentyl) ester (b) 1-deoxynojirimycin

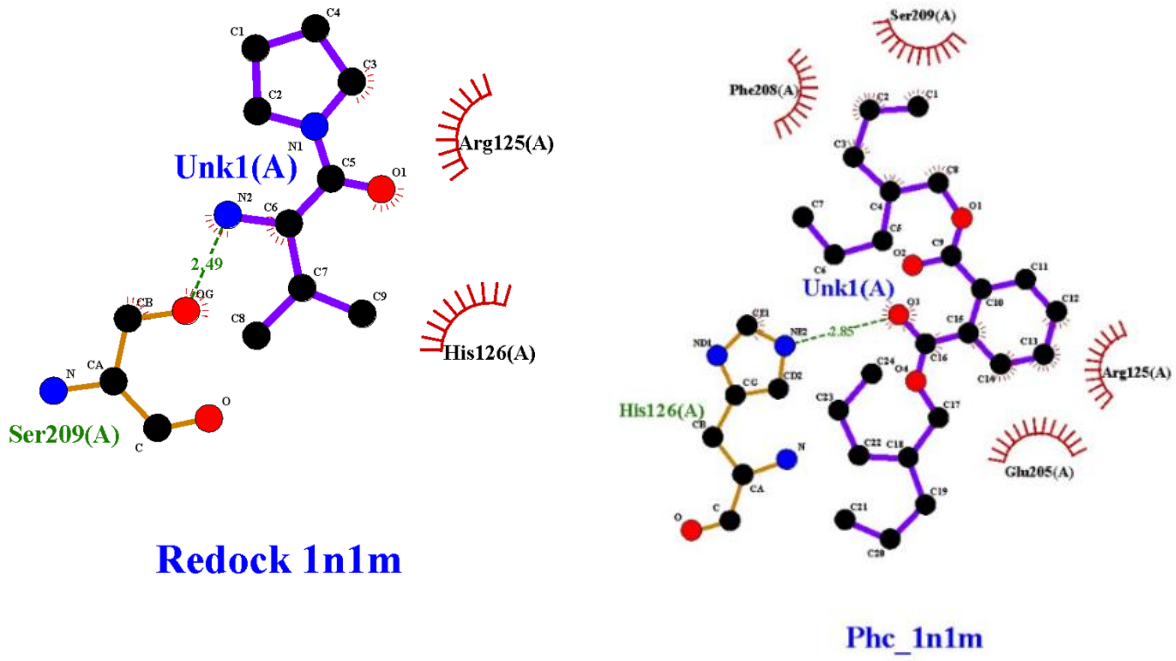
Table 2. Interaction between ligand and protein

	1-deoxinji Romicyn	**Phtalic acid, ester**	**Acarbose**
Amino acid	Trp485 Val444 Glu448 Arg445 Pro476	Trp485 Val444 - - - Arg449 Asn446 Ser443 Tyr447 Arg477 Asp406	- Val444 Glu448 Arg445 Pro476 Arg449 - - - - - Ile475 His489 Glu479 Asn488 Tyr492
Number of bonds	5	2/6	4/6
Docking score	-77,124	-61,606	149,626

Visualization of the molecular docking results on the phthalic acid molecule, di(2-propylpentyl) ester, against the dipeptidyl peptidase-4 (1N1M) receptor, is shown in **Figure 6**. The interactions are hydrogen bonds with amino acid His126 and hydrophobic interactions with amino acids Glu 205, Arg125, Ser209, and Phe208. Meanwhile, the original ligand has hydrogen bonds with amino acid Ser209 and hydrophobic interactions with Arg125 and His126. These results are in line with the findings by [30], who concluded that the interaction formed between the ligand and the receptor is right on the active side of the DPP-4 enzyme, namely Glu205, Glu206, Asn710, Tyr662, Arg125, Ser630, Phe357, Tyr666, Tyr547, and Ser209. Hydrogen bonds dominate the interaction that occurs between the ligand and the receptor.

The docking analysis and two-dimensional representation of the phthalic acid compound, di(2-propylpentyl) ester, indicated superior inhibition against the dipeptidyl peptidase-4 receptor compared to the alpha-glucosidase receptor. Earlier research has indicated that the yacon plant exhibits inhibitory properties against the alpha-glucosidase enzyme. This is attributed to the isolated compound being **nyctose** [31], which results in a mechanism different from that of the present study. Both in vitro and in vivo experiments need to be conducted to gather additional supporting evidence regarding the yacon plant's potential as an antidiabetic agent.

Phthalic acid molecule, di(2-propylpentyl) ester docked with 1N1M receptor (**Table 3**) has amino acid interaction Ser209, Arg125, His126, similar to the interaction that occurs in the original ligand so that the binding energy is low and more stable compared to valine. In the 1N1M receptor, amino acid residues Glu205, Glu206, Arg356, Phe357, Arg358, Lys554, Trp629, Tyr631, Tyr662, and Tyr666 are some amino acids that contribute to hydrogen bonds and hydrophobic interactions [32].



(a) (b)

Figure 6. 2D visualization of the docking results of the 1N1M receptor (a) Valine (b) phthalic acid, di(2-propylpentyl) ester

Table 3. Interaction of phthalic acid molecules, di(2-propylpentyl) ester with dipeptidyl peptidase-4 receptor

	Valine	**Phthalic acid, di(2-propylpentyl) ester**
Amino acid	Ser209 Arg125 His126	Ser209 Arg125 His 126 Glu 205 Phe208
Amino acid amount	3	3/2
Docking score	-75.048	-86.945

In literature studies, substances found in red ginger, which may act as inhibitors of SARS-CoV-2, comprise cyanin, gingerenone A, and quercetin, as explored through the In-Silico method [33]. Computer-aided drug design (CADD) plays a crucial role in developing new medications, as it accelerates the process by utilizing prior knowledge about how ligands interact with receptors and their structural refinement and synthesis. Key pharmacological characteristics, including absorption, distribution, metabolism, excretion, and toxicity, are vital for successfully creating new drugs. Additionally, numerous models based on machine learning have been created as biological data continues to grow [34].

Conclusion

The phytochemical analysis of *Cosmos caudatus* and *Smallanthus sonchifolius* indicates their potential as

natural drugs, as suggested by an in silico study. The docking scores for the active compounds in knicker and yacon leaves, specifically Diisooctyl Phthalate, showed antioxidant potential, with an average score of -81.07, representing a stable form. The isolated compound, phthalic acid di(2-propyl pentyl) ester, demonstrated a docking score of -61.606 with the alpha-glucosidase receptor and -86.945 with the dipeptidyl peptidase-4 receptor. The in silico findings suggest that this isolated compound acts as an antidiabetic by inhibiting the dipeptidyl peptidase-4 receptor, which significantly lowers blood sugar levels.

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Conflict of interest

The authors declare that they have no conflicts of interest regarding the publication of this manuscript.

Athors Contributions

substantial contributions (T.Irianti, K. Pangeran, B. Pratama); analysis (T.Irianti, K. Pangeran, B. Pratama, H.Purnomo, Ritmaleni), interpretation of data (T.Irianti, K. Pangeran, B. Pratama, H.Purnomo, Ritmaleni).

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Using artificial intelligence chatbots

There was no use of artificial intelligence in the making of this article.

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