In Vivo Activities and In Silico Study of Jackfruit Seeds (Artocarpus heterophyllus Lam.) on the Reduction of Blood Sugar Levels of Gestational Diabetes Rate Induced by Streptozotocin

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Abstract

BACKGROUND: Jackfruit Seeds (Artocarpus heterophyllus Lam.) are plants that are thought to be able to reduce blood sugar levels.

AIM: The purpose of this study was to prove the activity of jackfruit seeds in reducing blood glucose levels in gestational diabetic rats induced by streptozotocin and in silico study virtual screening through molecular docking to find out the compounds in jackfruit seeds that have interaction with sulfonylurea receptors.

METHODS: The animals used in this study were Sprague Dawley strain pregnant female rats which were divided into six groups, namely the normal control group, negative control, positive control, various dose groups (100 mg/kg BW, 200 mg/kg BW, 400 mg/kg BW). After the rat was pregnant, the rats were induced first with streptozotocin so that the rats had hyperglycemia. Blood glucose levels were measured on the 14th day after treatment. The data obtained were statistically tested by one-way ANOVA test followed by the HSD Tukey test.

RESULTS: The results showed that all groups of ethanol extract 70% of jackfruit seeds could reduce blood glucose levels. The biggest decrease in blood glucose levels occurred at dose 3 with a dose of 400 mg/kg BW which was 61.73%, comparable to positive control glibenclamide. The results of virtual screening with molecular docking showed that betacarotene epoxide compounds have better affinity than glibenclamide as a comparative compound.

CONCLUSION: It can be concluded that jackfruit seeds beta-carotene epoxide has the potential to reduce blood sugar levels by inducing insulin secretion.

Introduction

Diabetes Mellitus (DM) is a degenerative disease in which the number of its patients are rising over years. According to WHO, DM was ranked at seventh place for the total death of non-contagious disease. Also, DM was considered one of the most common chronic disease in the 21st century. The prevalence of DM doubled in the past three decades. Nearly 1 out of 10 adult people suffers DM. According to the International Diabetes Federation (IDF) in 2011, 366 million people suffer from DM, and by estimation, the number would rise to 552 million cases by 2030. Between 2010 and 2030, DM cases in adults will increase by 69% and 20% in developing and developed countries, respectively [1].

Diabetes Mellitus can occur in pregnant women, as there will be changes in their carbohydrate, protein, and fat metabolism. These physiological changes affect their carbohydrate metabolism because of the placental hormone that is resistance to insulin. These changes result in diabetogenic pregnancy, and by the time the gestation period start to mature, many factors could result in an imbalance of carbohydrate metabolism; thus, disturbance of glucose tolerance occurs.

According to American Diabetes Association (ADA) Guidelines, a woman is considered at higher
risk of having gestational diabetes if one or more
criteria is/are met: obesity, history of previous
gestational diabetes, glucose or glucosuria
intolerance, related to close family members with
Type II Diabetes Mellitus.

A mother who suffers from gestational
diabetes will not only affect herself but also the foetus. Gestational diabetes could affect the mother to later develop hyperglycaemia and several other complications such as retinopathy, nephropathy, and neuropathy; while the foetus could have respiratory problems, congenital abnormalities, and macrosomia. Congenital abnormalities are considered as the main cause for perinatal mortalities. One of the therapies in the treatment of GDM is using oral antidiabetic drugs that can be done with one type of drug or a combination of drugs, one of which is a sulfonylurea drug. Sulfonylurea drugs are a choice of drugs given to new adult diabetics with normal weight and less and have never experienced previous ketoacidosis disorders such as gestational diabetes mellitus. This class of drugs has a mechanism of action by increasing insulin secretion in the pancreatic gland, so it is only effective in diabetics whose pancreatic β cells are still functioning properly and can reduce adult blood sugar levels (A1c) by 1-2% which are commonly used 1 up to 2 times a day to regulate and control blood glucose levels post prandial [2], [3].

However, a study states that sulfonylureas can cause cardiovascular disease and with side effects of disorders of the gastrointestinal tract and central nervous system in the form of vertigo, confusion, ataxia and others [3]. Therefore, one alternative that can be used to reduce blood glucose levels in the body is by using herbal medicines such as jackfruit plants. Jackfruit is one of the many plants found in Indonesia and has many benefits, one of which is reducing blood glucose levels [4].

Management of Gestational Diabetes could be done both by pharmacological and non-pharmacological intervention. Non-pharmacological intervention includes a change in diet, physical activities and weight maintenance. Orally taken anti-diabetes drugs and insulin injection covers for the pharmacological intervention. The use of anti-diabetes drugs in short and long-term can cause side effects on an internal organ, and if left untreated, would create complications and thus increasing the medical expense. There need to be considerations on traditional alternative treatment that use natural ingredients that are inexpensive, safe, and cause little to no side effects.

Jackfruit is a plant with many medicinal properties, and have been used by indigenous people to treat various diseases for generations; an example of this is the anti-bacterial properties of jackfruit stem and root barks. Another medicinal property is jackfruit leaf extract in a dose of 500 mg/kg of body weight could lower glucose level in blood. Osmani et al., (2009) conducted a study of ethanol extract of seeds of the jackfruit Artocarpus heterophyllus Lam. has the ability to reduce blood glucose levels in diabetic rats that have been induced by streptozotocin at a dose of 400 mg/kg BW [5]. In an experiment carried out by Moura et al., (2018), ethanol extract is taken from jackfruit (Artocarpus heterophyllus Lam.) possess the ability to reduce the hyperglycaemic level of mice at a dose of 50 milligrams per kilogram of body weight at a rate of 32.3% [6].

One of the natural ingredients that can be used as an alternative for anti-diabetes drugs is jackfruit seeds. Research on the use of jackfruit seeds against gestational antiabetic mellitus is still not widely done. Based on the explanation above, an experiment was conducted on the activities of 70% ethanol extract taken from jackfruit seeds in lowering blood glucose level in gestationally diabetic streptozotocin-induced rats. The compounds in jackfruit seeds are used as candidates in lowering blood glucose levels or in the treatment of diabetes and have activity in reducing blood glucose compared to glibenclamide, but it is not known which compound is the most efficacious as a diabetes drug including terpenoids (carotene), flavonoids and phytosterols (β-sitosterol) [5], [7]. Therefore, one way that can be done to find out the optimal compounds in the treatment of diabetes is through in silico virtual screening by simulations molecular docking. Molecular docking is a device that can be used to study the interactions that occur from a molecular complex. Molecular docking helps in studying drug or ligand interactions with receptors or proteins. Molecular docking is conducted by identifying the corresponding active site of the receptor / protein, obtaining the best geometry of the receptor ligand and calculating the interaction energy of each different ligand for designing a more effective ligand. To perform molecular docking, the first thing required is a three-dimensional structure of ligand and receptor. Virtual screening is a computational technique in the design of new computer-based drugs (in silico) to identify the structures most likely to bind to a targeted drug, usually a protein receptor [8].

Material and Methods

Materials

Micropipets, centrifuge, microtube, vacuette, spectrophotometer clinical vortex, the material used in this study was jackfruit seeds obtained from BALITTRO and has been determined at the LIPI, ethanol 70%, Na CMC, reagent Mayer, Dragendorf, methanol, HCl 2N, FeCl3, Streptozotocin (sigma), Gilbenclamide (kimia farma co).

Intel (R) Pentium (R) CPU specifications 987
Plant material

The fruit seeds Artocarpus heterophyllus has been collected from Indonesia Institute of Science (LIPI). The species for the proposed study was identified as Artocarpsm heterophyllus Lam by Dr. Joeni Setijo Rahajoe, Botanist Nomor: 758/IPH.1.01/f/07/III/2018.

Preparation of Artocarpus heterophyllus seeds

The powder of seeds (1.7 kg) of Artocarpus heterophyllus, Extraction of jackfruit seeds use maceration because extraction in this way is a simple method of extraction and does not have the potential to damage plant active substances. Maseration of jackfruit seed powder weighed as much as 1.7 kg, then extracted with ethanol 70% solution as 10 L and soaked for 6 hours, then allowed to stand for 3 days protected from light accompanied by stirring which aims to flatten all the simplicia powder. The maserate obtained was then evaporated using a vacuum rotary evaporator to obtain 70% ethanol extract [10].

Animals

Male strain sparague dawley (SD) albino rats having weight 170- 200gm were kept in quarantine for 10 days under standard husbandry conditions. The study was permitted by the Institution Animal Ethical Committee No: 02/18.05/003.

The animals used in this study were Sprague Dawley strain pregnant female rats which were divided into six groups, namely the normal control group, negative control, positive control, various dose groups (100 mg/kg body weight, 200 mg/kg body weight, 400 mg/kg body weight). After the rat was pregnant, the rats were induced first with streptozotocin so that the rats had hyperglycemia. Blood glucose levels were measured on the 14th day after treatment. The data obtained were statistically tested by one-way ANOVA test followed by the HSD Tukey test.

The preparation of receptor structures (PDB ID: 2FF7) which have been downloaded through the Protein Data Bank with the site http://www.rcsb.org/pdb using YASARA with the aim of separating the natural residues and ligands contained in the receptor. The native ligand structure obtained was prepared using Marvin Sketch along with the ligand downloaded from PubChem through the site http://PubChem.ncbi.nlm.nih.gov. In the preparation of the ligand structure, pH was set at pH 7.4 to adjust the pH conditions of the in the human body or can be called the physiological pH of the body.

Method validation and re-docking using software PLANTS and YASARA to get the default binding site and RMSD (Root Mean Square Deviation) heavy atoms of the original receptors and ligands. Simulation Molecular docking (virtual screening) using PLANTS to find the best compounds were analyzed through value best score ChemPLP / value of free energy (ΔG) the lowest. Visualization of Molecular Docking Results uses Discovery Studio Visualizer which will show the interactions that occurred between ligands and receptors [16].

Data Analyzed

The data of in vivo activities were analyzed by statistically, first tested for normality and homogeneity. After that, there was a direct direction analysis of variance (ANOVA) with a 95% significance level (p <0.05). then it was seen that there were no significant differences if there were significant differences, then continued with the Tukey test.

Results

In vivo activities

Before conducting the research, plant determination test needs to be conducted first to determine the exact plant variety that will be used. The plant determination test was carried out in “Herbarium Bogoriense”, Botanical Sector of LIPI Biological Research Centre in Cibinong. The result from the determination test shows that the simplistic that will be used is Artocarpus heterophyllus Lam., locally known as “nangka” and from Moraceae family.

Table 1: Results of Jackfruit Seeds Extraction

| No | Exemplar                        | Result  |
|----|---------------------------------|---------|
| 1  | Fresh Jackfruit Seeds           | 4 kg    |
| 2  | Powdered Jackfruit Seeds        | 1.700 kg|
| 3  | Thick 70% Ethanol Extract of JS | 171.39 g|

Notes: JS = Jackfruit seeds.
On Table 1 above, it can be observed that there was some weight shrinkage of simplistic, starting from fresh jackfruit seeds into thick 70% ethanol extract of jackfruit seeds. The weight shrinkage occurred due to sorting, drying, and extracting process.

To establish the characteristic of thick 70% ethanol extract of jackfruit seeds, an organoleptic test was conducted can be seen in Table 2.

Table 2: Results of Thick 70% Ethanol Extract of Jackfruit Seeds

| No | Exemplar                          | Smell | Taste | Colour |
|----|-----------------------------------|-------|-------|--------|
| 1  | Powdered Jackfruit Seeds          | Particular | Particular | Light Brown |
| 2  | Thick 70% Ethanol Extract of JS   | Particular | Bitter | Brown |

Notes: JS = Jackfruit Seeds.

Organoleptic tests were conducted to establish the characteristic of the thick 70% ethanol extract of jackfruit seeds that includes smell, taste, and colour. From the test, it was concluded that thick 70% jackfruit seeds’ ethanol extract permeates a particular and proprietary smell, with a bitter taste and brown colour, in a viscous or thick liquid.

Table 3: Results of Phytochemical Filtering of Thick 70% Ethanol Extract of Jackfruit Seeds

| No | Secondary Metabolite | Results |
|----|----------------------|---------|
| 1  | Alkaloid             | +       |
| 2  | Flavonoid            | +       |
| 3  | Tannin               | +       |
| 4  | Steroid              | +       |
| 5  | Saponin              | +       |
| 6  | Terpenoid            | +       |

Notes: (+) = substance presence.

Phytochemical filtering tests carried out to determine the chemical substances that are present such as alkaloid, tannin, steroid, saponin and terpenoid that are present in thick 70% jackfruit seeds ethanol extract. The acquired result shows that the extract does contain chemical substances above (Table 3).

Table 4: Results of Yield and Drying Shrinkage of Thick 70% Ethanol Extract of Jackfruit Seeds

| No | Exemplar                          | Result   |
|----|-----------------------------------|----------|
| 1  | Thick 70% Ethanol Extract of Jackfruit Seeds | 10.08%   |
| 2  | Shrinkage Rate of Thick 70% Ethanol Extract of Jackfruit Seeds | 9.3%     |

Establishment of shrinkage rate was carried out in order to know how much substances were lost during the drying process. The requirements for shrinkage rate according to the standard parameter is < 10%. The result from the conducted test shows that the shrinkage rate of ethanol extract taken from jackfruit seeds fulfilled the criteria, with the shrinkage rate of < 10% (Table 4).

The rats that were used in this experiment is the white laboratory rats (Rattus norvegicus) from the Sprague Dawley strain, acquired from Laboratorium Non-Romianis and Satwa Harapan Fakultas Peternakan IPB. 24 rats that ranged at the age of 2-3 months were divided into six groups with each group consisted of 4 individual rats with ± 200-gram body weight (Table 5). The rats were acclimatized before being put in the experiment by putting them in cages for 14 days, so as to provide the animals with a familiar environment, and also to increase their body weight by giving them controlled foods and drinks, in accordance to the 02/18.05/003 Ethical Approval standard.

Table 4: Body Weight of Rats before pregnancy and after pregnancy

| Groups | Body Weight (gram) |
|--------|--------------------|
| Normal | 197  198  200  202 |
| STZ    | 197  201  201  204 |
| Glibenclamide | 199  200  211 |
| Dose I | 200  202  202  208 |
| Dose II | 200  202  202  208 |
| Dose III | 200  202  202  208 |

Before the test, an observation of the rats’ oestrus period was conducted. During the height of their oestrus period, the activities of the rats were high; there were also physiological changes to them such as flowering and inflammation of the vagina. The test animals were made to mate with each other at noon with the ratio of one male per four female rats. Pregnant rats were then marked by a vaginal plug that also signifies day 0 of pregnancy and randomly sorted in six groups.

After pregnancy, the rats were induced with streptozotocin (STZ) so as to make them hyperglycaemic. STZ entered their β pancreatic cell from the glucose transporter (GLUT2). Their β pancreatic cell was damaged by the streptozotocin (STZ) so as to make them hyperglycaemic. STZ induced to confirm hyperglycaemia. Based on the test of blood sugar levels on negative, positive, and test control rats, a median of 350.9 ± 41.82 mg/dL (Appendix 12) was acquired. The rats were considered hyperglycaemic when their blood sugar levels measured at > 200 mg/dL.

As observed in Figure 1, the admission of 70% ethanol extract of jackfruit seeds on all three dosages shows that it can lower blood glucose level. According to statistical testing on blood sugar levels of the test groups, a normal test result of value P = 0.054
> \alpha (0.05) \) of normally distributed data was acquired. An acquired result of the homogeneity test of value \( P = 0.082 > \alpha (0.05) \) shows the data is homogenous, which were then analysed with one-way ANOVA test. The ANOVA one-way test results on the final blood glucose level yield the value \( P = 0.000 < \alpha (0.05) \), which shows that there are significant distinctions on each test groups.

Further analysis of the data using Tukey test was carried in order to determine if there are differences in the final and significant reduction of blood glucose level on each test groups. From the Tukey table, it was observed that the measurement result shows \( P < 0.05 \), which means there are significance differences in the drop rate of blood sugar level on a positive control test group with dosage 1 and 2, but no distinct and significant reduction observable on positive control test group with dosage 3; this clearly shows that 70% jackfruit ethanol extract with dosage of 400 mg/kg of body weight have much more effect than dosage 1 or 2. The effect of dosage 3 is similar to glibenclamide drug administered at 0.51 milligram per kilogram of body weight. The data for statistical testing can be seen in

![Figure 1: Blood Glucose Level (mg/dL)](image)

Table 5: Median Percentage on the Reduction of Blood Glucose Level of Rats

| No | Group                  | Percentage of Blood Glucose Level Drop ± SD (σ)       |
|----|------------------------|-------------------------------------------------------|
| 1  | Normal                 | 1.08 ± 2.91                                           |
| 2  | STZ                    | -0.92 ± 1.02                                          |
| 3  | Glibenclamide (0.51 mg/kgBB) | 63.68 ± 1.75                                      |
| 4  | Dose 1 (100 mg/kgBB)   | 51.01 ± 3.32                                          |
| 5  | Dose 2 (200 mg/kgBB)   | 53.49 ± 5.42                                          |
| 6  | Dose 3 (400 mg/kgBB)   | 61.73 ± 1.14                                          |

The result of the blood sample taken at early and later stage of the research regarding blood glucose levels that were statistically processed are a normal group, negative and positive group, and test group on every three dosages. A percentage on the median rate of blood glucose level reduction was made. The median percentage on blood glucose level reduction are: normal group with -1.68 ± 1.61; negative group with -0.92 ± 1.02; positive group with 63.50 ± 2.88; dose 1 group with 51.015 ± 3.32; dose 2 group with 53.49 ± 5.42; and dose 3 group with 62.73 ± 1.14.

As can be observed in Table 5, 70% ethanol extract taken from jackfruit seeds is beneficial in lowering glucose level with performance similar to glibenclamide on positive control test. The dosage (400 milligrams per kilogram of body weight) of jackfruit seeds ethanol extract used in this research have the ability to reduce the amount of glucose in blood on gestationally diabetic rats with the rate as high as 61.73%. The reduction of blood glucose level correlates with activities of flavonoid substance in jackfruit seeds. The substances content in jackfruit seeds is flavonoid, alkaloid, saponin, steroid and terpenoid.

The result of this study shows that 70% ethanol extract taken from jackfruit seeds with dose variants (100 mg, 200 mg, 400 mg per kilogram of body weight) possess activities that can lower the amount of glucose in the blood. The percentage of blood glucose level reduction on dose 1 is 51.01%; dose 2 is 53.49%; dose 3 is 61.73%—with the percentage of glibenclamide is measured at 63.68%. It can be seen that the administration of dosage 3 has greater impacts compared to dosage 1 or 2, but similar in reduction rate with glibenclamide drug.

**In silico study**

Sulfonylurea 1 receptor with PDB ID: 2FF7 has a resolution value of 1.6 Å. with 243 amino acid residues. This receptor binds to 1 ligand, ADP (Adenosine-5'-Diphosphate) as a native ligand. The lower resolution value (less than 3 Å) on a receptor can affect the stability of the receptor when doing molecular docking, so if the resolution value is lower, the receptor stability will be better and the resolution value in the PDB code used is the protein structure that has similarity of poses to the X-ray original/protein-protein structure [11].

Validation of method by re-docking using software PLANTS with native ligands and their receptors aimed to find out which methods and applications were valid or not and look for binding sites of receptors used. The results of the re-docking obtained by the binding site were in coordinates \( x, y, \) and \( z = 159.209, 65.6242, \) -67.8247 and the radius was 11.7839 Å. Re-docking obtained by Score ChemPLP (ΔG) as free energy results were of -99.1334 kcal/mol. Then the results were analyzed through YASARA by analyzed the RMSD (Root Mean Square Deviation) heavy atoms value is 1.2070 Å.

Figure 2 is the result of validation; it can be seen that there are 2 compounds with different colours. The compound with the magenta atom is a ligand structure X-ray as native ligand while the structure atom in yellow is a ligand structure resulting from docking.
The interaction of hydrogen when the interaction distance is smaller, the stability that is formed becomes stronger and vice versa. Table 7 shows that the ligand β-carotene 5,6α has a small range of hydrophobic interactions and even a distance of less than 3.00 Å which causes high stability of the ligand to the receptor when compared to glibenclamide-receptors seen from a bond distance.

Table 6: Results of Simulations Molecular Docking the Standard Ligand (Glibenclamide) and Ligands of Jackfruit seeds by using SUR1 Software PLANTS

| Ligands | Score ChemPLP/ΔG (kcal/mol) |
|---------|-----------------------------|
| 1 Glibenclamide  | -99.1334                   |
| 2 glibenclamide (Comparative ligand) | -97.5607 |
| 3 β-Phenylnaphtalen | -82.8290 |
| 4 Alpanen | -78.3627                   |
| 5 Artoncin | -81.6042                   |
| 6 Antonin A | -83.0916                   |
| 7 Antonin B | -83.0404                   |
| 8 Brosimone I | -81.3246 |
| 9 Cudrafavon B | -79.2615 |
| 10 Cudrafavon C | -92.0041 |
| 11 Cyclohexylphenol | -84.2288 |
| 12 Cyclohexylphenol diazet | -85.7945 |
| 13 Cyclohexylphenol peracetat | -75.4067 |
| 14 Kuwanon | -81.4849                   |
| 15 Norartocarpin | -83.3682 |
| 16 β-sitosterol | -84.7237 |
| 17 o-Zaarctene | -84.0042 |
| 18 β-karotenol,6,6α | -161.381 |
| 19 β-epoxidecarotenone | -157.069 |
| 20 Crocetin | -78.2024                  |

Table 7: Results of Bond Type, Atom in Function Groups, Amino Acid Residues Binding, Distance of Bonds Between SUR1 Receptors and Ligands Using Software Discovery Studio Visualizer

| Ligands | Bond Type | Interaction Distance | Bond Type | Atom in Functional Groups Binding | Amino Acid Residues Binding | Distance of Bond (Å) |
|---------|------------|----------------------|------------|----------------------------------|---------------------------|---------------------|
| 1 Glibenclamide Hydrophobic Interaction | Atomic C in Benzene (D) | Ile681 (A) | 4.65 | Atomic C in Benzene (D) | Ile651 (A) | 4.65 |
| 2 β-carotene 5,6α-epoxide | Hydrophobic interactions | Atom H20 (D) | O(CH3) | Asp630 (A) | 2.8 |

Discussion

The RMSD heavy atoms value (less than 2.0 Å) shows the deviation value between one ligand conformation structures with ligands x-ray (original). If the deviation gets smaller, the smaller the error in the prediction of ligand interactions with the protein can be said and the ligation conformation with the original ligand has the same and parallel structure and atom so that the RMSD value can reach 0 Å. However, if the value of deviations that occur is large, the greater the error in predicting ligand interactions with proteins, in other words, the ligand conformation and the original ligand have structures and atoms that are not the same, not parallel and far apart. RMSD is also used to determine whether the prediction of the bond mode is successful and important in the program validation process docking [11]. Validation results show that the RMSD value heavy atoms of 1.2070 Å are still in the range of RMSD values that are allowed. This happens because there were a structure and atomic conformation of the best ligand has a position that is not the same and not parallel to the original ligand structure so that the RMSD values are heavy atoms large. Validation of protocol docking aimed at look for the compatible method of protocol docking. It can be seen from the RMSD heavy atoms less than 2.0 Å. This method compatible for PDB code 2FF7 as the receptor that has RMSD 1.2070 Å. So, the...
coordinate of binding site was able to be used as coordinate binding site of virtual screening of compounds in jackfruit seeds by molecular docking.

Virtual screening of compounds in jackfruit seeds conducted using the same binding site from the results of the validation aims for the 18 ligands molecular tethering process of jackfruit seeds and 1 comparison ligand, the default site centre bindings are used which are x, y and z = coordinates 159,209, 65,6242, -67,8247 and the radius is 11,7839 Å. The results of the simulation are in the form of files that will show Score ChemPLP (ΔG) in each compound that is docking and will be a parameter in the analysis of results. Analysis of results was carried out through screening best score ChemPLP of each compound docking by choosing a compound with conformation that has the free energy value (ΔG) lowest. The value of the free energy produced when the receptor-ligand complex was formed can show the affinity of the ligand to its receptor. If the ligand affinity for the receptor is high, the value of the free energy is smaller, whereas if the affinity is small, the value of free energy is greater.

The Gibbs free energy values evaluated and are the result of simulation of docking using sulfonilyurea receptors. The Gibbs free energy value used is the lowest value, because the low Gibbs free energy value shows a high affinity in the molecular tethering process. If the Gibbs free energy value has a low value, the ligand-receptor binding affinity gets bigger and vice versa if the Gibbs free energy value is greater, the binding affinity will be lower. In the table 6 can be observed that the lowest Gibbs free energy value is in the ligand of jackfruit seed compound which is compound β-carotene 5,6α-epoxide with value scores ChemPLP were -161,381 kcal/mol while the original ligands were only -99,1334 kcal/mol and comparative ligands were -97,5607 kcal/mol. These results indicated that the interaction between the β-carotene 5,6α-epoxide compound with the sulfonylurea 1 receptor is better than the original ligand or glibenclamide and has the potential as a gestational antidiabetic mellitus.

Visualization carried out was a visualization of the ligand β-carotene 5,6α-epoxide to the receptor. Interactions will be better if the Score ChemPLP / Gibbs free energy the lower (negative) as it relates to affinity ligand-receptor which is getting stronger and it can be said interaction ligand-receptor is very strong, but on the contrary if the Score ChemPLP / free energy Gibbs higher (positive) will result in low ligand-receptor affinity [12].

In the interactions that occur between ligands and receptors, there are only two types of interactions, hydrogen interactions and hydrophobic interactions. Hydrogen interaction only occurs in glibenclamide-receptor ligands (Figure 3) and does not occur in the ligands of β-carotene 5,6α-epoxide (Figure 4).

In the ligands of hydrogen interaction glibenclamide receptors only occur on 2 H atoms, namely the functional groups -OCH$_3$ and -CONH which acts as atomic donors to two amino acids namely Asp630 and Ser509 with bonding distances of 2.8 Å and 1.22 Å. Limitation of bond distance in hydrogen interactions is 3.50 Å which is a determinant in maintaining the stability of ligand-receptor conformation [13].

The smaller the distance, the stronger the ligand-receptor stability, the greater the distance, the smaller the ligand-receptor stability. The second interaction is the hydrophobic interaction which is also an interaction that can determine the stability of the ligand-receptor. Hydrophobic interactions have power in the process of combining non-polar ligand regions with non-polar receptor regions which results in the formation of structures quasi-crystalline (icebergs) insoluble in water and surrounding water molecules through hydrogen bonds [14]. This hydrophobic bond has a bond strength of only 1 kcal/mol, but due to the presence of water molecules surrounding it, this bond becomes stable. Limitation of distance on hydrophobic interactions is 5.00 Å [15].

In conclusion, the ethanol extract 70% jackfruit seeds at a dose of 1 (100 mg/kgBB), dose 2 (200 mg/kg body weight), and dose 3 (400 mg/kg body weight) for 14 days was able to reduce blood glucose levels in gestational diabetic rats. The highest
decrease in blood glucose levels occurred at dose 3 of 61, 73%, comparable to the positive control of glibenclamide which was 63.68%. Compounds found in jackfruit seeds (Artocarpus heterophyllus L.) namely β-carotene-epoxide5,6α were able to interact with sulfonylurea 1 (SUR1) receptors well compared to glibenclamide with the lowest Gibbs free energy value of -161,381 kcal/mol while glibenclamide -97,5607 kcal/mol. It can be concluded that the ligand has Gibbs free energy which is better than Glibenclamide and can be used as a new drug candidate in the treatment of gestational diabetes mellitus.

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