**ABSTRACT**

**Background:** Interleukin 12 can destroy insulin-producing cells, suppresses IL4 production, and can stimulate the formation of Thelper1. Quercetin is a flavonoid suitable the lead compound for development of safe anti-diabetic agent because its anti-diabetic effect and protective effect in pancreas track.

**Objective:** This research aims to study the docking models of certain flavonoids and to predict the quercetin and triterpene derivatives inhibition activity on Interleukin12.

**Method:** The molecular docking method was used using the PyRx program with the Autodock Vina menu.

**Results:** IL-12 bond affinity with Dextromethoorpene results -7 kcal/mol as the highest affinity value energy while the lowest energy is -6.1 kcal/mol, IL-12 bond affinity value with Quercetin with the highest affinity value energy is -9 kcal/mol, and the lowest energy is -7.8 kcal/mol. The affinity value IL-12 bond and triterpene with the highest affinity value is energy -7.9 kcal/mol and the lowest energy is -7.4 kcal/mol.

**Conclusion:** Quercetin, has hydrogen bonds and hydrophobic bonds, where the ligand of the Quercetin compound is the ligand that has the ability to form the best interactions and bonds with IL-12 receptors (4OG9).

**Keywords:** IL-12, quercetin, diabetes mellitus, docking

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**INFO ARTIKEL**

**ARTICLE HISTORY:**
Artikel diterima: 17 Agustus 2023  
Artikel direvisi: 21 Agustus 2023  
Artikel disetujui: 22 Agustus 2023

**KORESPONDEN**
Marina Magdalena Riyaniarti Estri Wuryandari, mm.riyaniarti@iik.ac.id, Orcid ID:https://orcid.org/0000-0002-4965-123X

**ORIGINAL ARTICLE**
Halaman: 217 - 223  
DOI: https://doi.org/10.30989/mik.v12i2.1060

Penerbit: Universitas Jenderal Achmad Yani Yogyakarta, Indonesia  
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**ABSTRAK**

**Latar Belakang:** Interleukin 12 dapat menghancurkan sel penghasil insulin, menekan produksi IL4, dan dapat merangsang terbentuknya Thelper1. Quercetin adalah flavonoid sebagai senyawa utama untuk pengembangan agen antidiabetes aman, karena efek antidiabetes dan efek perlindungan pada jalur pankreas.

**Tujuan:** Untuk mempelajari model docking flavonoid tertentu dan memprediksi aktivitas penghambatan terhadap quercetin terhadap Interleukin 12.

**Metode:** Molekuler Docking dengan menggunakan PyRx menggunakan program Autodock Vina.

**Hasil:** Afinitas interaksi IL-12 dengan Dextromethoorpene memiliki energi seminimum mungkin yaitu -7 kcal/mol dan yang paling rendah atau energi maksimum yaitu -6,1 kcal/mol, nilai afinitas ikatan IL-12 dengan Quercetin dengan nilai afinitas tertinggi yaitu energi seminimum mungkin yaitu -9 kcal/mol dan yang paling rendah atau energi maksimum yaitu -7,8 kcal/mol dan Nilai afinitas ikatan IL-12 dengan Triterpene nilai afinitas antara ikatan IL-12 dengan triterpene dengan nilai afinitas tertinggi yaitu energi seminimum mungkin yaitu -7,9 kcal/mol dan yang paling rendah atau energi maksimum yaitu -7,4 kcal/mol.

**Kesimpulan:** Quercetin memiliki ikatan hidrogen dan ikatan hidrofobik, dimana ligan dari senyawa Quercetin merupakan ligan yang memiliki kemampuan untuk membentuk interaksi dan ikatan terbaik dengan reseptor IL-12 (4OG9).

**Kata kunci:** IL-12, Quercetin, Diabetes Millitus, Docking
INTRODUCTION

The small proteins, cytokines, are mediators and regulators of immunity, inflammation and hematopoiesis. They are one of a number of substances produced by certain cells of the immune system that carry signals between local cells, resulting in effects on other cell as a result of the immune system's stimulus response. Interleukin 12 is a cytokine secreted by macrophage cells, dendrite cells, and neutrophils that is directly triggered by the presence of lipopolysaccharides or pathogenic microorganisms that enter the body.\(^1\) The role of the cytokine interleukin 12 is proven to be an interleukin that regulates the intra-cellular immunity center that activates NK cells, which are the main essential mediators to convert Thelper 0 into Thelper 1, and can directly trigger the production of IFN-\(\gamma\) by Thelper1 cells and NK cells.\(^2\) IFN-\(\gamma\) is a glycoprotein; an activator for monoclar phagocytes known to contain antiviral effects, produced by NK cells. While NK cells as triggers are cytokines produced by macrophages in the form of TNF-\(\alpha\) and interleukin 12 and IFN-\(\gamma\) itself.\(^3\)

Diabetes is a metabolic disease classified by hyperglycemia due to effects on insulin secretion, insulin action, or both. Chronic hyperglycemia in diabetes is strongly associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, innervation, heart, and blood vessels.\(^4\) At the same time, elevated blood glucose levels can affect changes in estimated Glomerular Filtration Rate (GFR) in patients with diabetes mellitus.\(^5\)

IFN-\(\gamma\) seems to have an important role in the development of insulin dependent diabetes mellitus (IDDM). Interleukin 12 is an interleukin which has the nature of destroying insulin-producing cells that can affect glucose levels in human blood. In addition, IL-12 can also suppress the production of IL4, and it can stimulate the formation of Thelper1 which produces pro-inflammatory cytokines.\(^6,7,8\)

Interleukin-12 (IL-12) is a pro-inflammatory cytokine and increased in type 2 DM contributes to the occurrence of inflammation to the development of atherosclerotic plaques.\(^9,10\)

Moringa oleifera is a plant that contains many active compounds that have a function as an antidote to Reactive oxygen species by increasing endogenous antioxidant enzymes which have a central role in dealing with oxidative stress.\(^3,11\) Moringa oleifera can also inhibit proinflammation through the TLR3 and TLR4 pathways while restoring naive T reg cells.\(^12\)

DM patients require pharmacotherapy such as injected insulin or oral antidiabetic drugs, but unfortunately all of these drugs can have dangerous side effects.\(^6,7\)

Some flavonoids including quercetin-3-glycoside derived from plants have a function to regulate blood sugar levels. 4OG9 affects glucose intake in the small intestine mucosa leading the absorption time of glucose to the blood is longer which in turn can reduce blood sugar levels.\(^13,14\)
The affinity interaction between flavonoids and interleukin 12 can be observed using Structure-Based Drug Design (SBDD) where the three-dimensional structure of the drug target is used as a reference for developing herbal drugs. Recently, computer-aided drug design (CADD) techniques have developed rapidly.

Predicting the three-dimensional structure of the complex between the target protein and the drug candidate plays an important role in SBDD. Currently, many computer programs can be used to predict protein-ligand interactions, known as docking, such as GOLD, FlexX, Glide, DOCK, and AutoDock.\textsuperscript{15,16}

The affinity interaction between the Interleukin 12 Protein macromolecule and (4OG9) with each activation ligand, namely quercetin, triterpenes. As a control using the drug Dextrometorpan, it can be known through docking results using the PyRx program with the Autodock Vina menu, Specific Docking. It aims to predict whether the compound has activity before being tested.\textsuperscript{17}

**RESEARCH MATERIALS AND METHOD**

This study was molecular docking method using PyRx program with Autodock Vina menu.

**Materials**

The structure of IL-12 protein that has binded with ligands from Protein Databank (PDB), various quercetin and triterpene ligands test, and dextrometorpane control were the materials of the study.

**INSTRUMENT**

A processor speed of 1.86 GHz and a memory capacity of 2 GB with ArgusLab 4.0.1 software of computer was used as the instrument of this study.

**ANALYSIS RESULT**

Analysis of docking results includes free energy and hydrogen bonding between the ligand and the enzyme.

**RESULT AND DISCUSSION**

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Binding Affinity</th>
<th>rmsd/ub</th>
<th>Rmsd/lb</th>
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<tbody>
<tr>
<td>4OG9_Deks</td>
<td>-7</td>
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<td>0</td>
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<tr>
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<td>2.648</td>
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<tr>
<td>4OG9_Deks</td>
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<td>16.24</td>
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<tr>
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</table>

The table presents there are 9 predicted bond affinity values between IL-12 and triterpene bonds with the highest affinity value being the minimum possible energy of -7.9 kcal/mol and the lowest or maximum energy being -7.4 kcal/mol.
Afinitas Interaksi Antara Flavonoid Terhadap Sitokin Interleukin 12 Pada Penyakit Diabetes Militus.

Maria Magdalena Riyanti Estri Wuryandari, Ninis Yuliati, Ekawati Sulikno Saad A. Mohamed

Table 2. Binding affinity of IL-12 with Quercetin

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Binding Affinity</th>
<th>rmsd/ub</th>
<th>Rmsd/lb</th>
</tr>
</thead>
<tbody>
<tr>
<td>4OG9_Quercetin</td>
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<td>0</td>
</tr>
<tr>
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<td>2.288</td>
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From the table, it shows there are 9 predicted bond affinity values between IL-12 and Quercetin with the highest affinity value being the minimum possible energy of -9 kcal/mol and the lowest or maximum energy being 7.8 kcal/mol.

Table 3 presents there are 9 predicted bond affinity values between IL-12 and triterpene bonds with the highest affinity value being the minimum possible energy of -7.9 kcal/mol and the lowest or maximum energy being -7.4 kcal/mol. From the results, it can be shown in the interaction between IL-12 with quercetin where there is the highest affinity value which is the minimum possible energy of -9 kcal/mol and the lowest or maximum energy of -7.8 kcal/mol as the energy used higher than other ligands.
The fewer bond interactions that occur, the lower the bond affinity value formed. Hydrogen bonds are weak bonds formed as interactions of attraction between atoms that have electronegative properties with hydrogen atoms located on other atoms that have the same properties (electronegative).

Hydrogen bonds occur in a molecule with other molecules, an example that occurs in proteins is the bond between N and H. While hydrophobic bonds are bonds in molecules insoluble in water. Such bonds will occur in polypeptide chains that form folding such that non-polar groups will go inside, while polar groups will be on the outside so that the protein will be more stable in water. Thus, protein stability depends on hydrophobic bonds. Hydrophobic interaction occurs in the bond between the R-group with non-polar compounds to form a folding fold.\(^ {18}\)

The visualization results of the bond between IL-12 and dextromethorpene found no hydrogen bonds, whereas the number of hydrophobic interactions are 8, namely, Asparagine no 55, Glutamine no 5, Glutamine no 13 Arginine no 57, Alanine no 2, Leucine no 56 Methionine no 54, Lysine no 9. However, the visualization of the bond between IL-12 and quercetin found the number of hydrogen bonds as much as 4 bonds, with bond distances of 3.04 Å, 3.09 Å, 3.10 Å, 2.86 Å. The position of hydrogen interaction is Arganin 37, Histidine 70, and serine 168. There are 6 hydrophobic interactions, namely Glutamine no 62, Glutamine no 63, Proline no 207, Asparagine no 66, Valine no 68, and Threonine no 65. Furthermore, the visualization of the bond between IL-12 and triterpene found no hydrogen bonds, while the number of hydrophobic interactions is 12, namely, Tryptophan no 45, Tyrosine no 314, Tyrosine no 315, Serine no 316, Aspartic Acid no 312, Aspartic acid no 292, Arginine no 313, Cystine no 41, Glutamine no 311 Glutamine no 38, Threonine no 42, and Threonine at no 272.

CONCLUSION
In conclusion, the most improved interaction between the ligand and the Interleukin 12 receptor of the three compounds above is quercetin, as it has hydrogen bonds and hydrophobic bonds, where the ligand compound Quercetin is a ligand that has the ability to form the best interaction and bond with the IL-12 receptor (4OG9) because the quercetin compound has the highest affinity bond value of -9 kcal/mol. Meanwhile, the lowest bond is with the IL-12 inhibitor forming the lowest affinity value of -7.8 kcal/mol which is the energy used higher than other ligands. Thus, the bonds that make up the interaction
can be seen. The interaction between IL-12 receptor and quercetin compound has 4 hydrogen bonds, and 6 hydrophobic bonds. The fewer bond interactions that occur, the lower the affinity bond value formed. Hydrophobic bonds affect the stability of the protein. So that quercetin compounds can be used as a candidate for herbal medicine for therapy of patients with Diabetes Mellitus.  

Hence, quercetin compounds in Moringa plants are proven to be therapeutically active as anti-inflammatory based on the results of molecular docking.

THANK YOU

1. Laboratory. Computing of Brawijaya University Malang
2. Bhakti Wiyata Institute of Health Sciences Kediri

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