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Quercetin: the bioactive compound from *Allium cepa* L. as anti-inflammation based on in silico screening

Mohamad Amin[1,*], Kurniawan Setia Putra[2], Ihya Fakhrurizal Amin[3], Nanda Earlia[4], Dina Maulina[5], Betty Lukiati[1], Umie Lestari[1]

[1]Department of Biology, Faculty of Mathematics and Sciences, Universitas Negeri Malang, Indonesia
[2]Graduate School for Biology Education Study Program, Universitas Negeri Malang, Indonesia
[3]Faculty of Medicine, University of Indonesia, Indonesia
[4]Graduate School of Mathematics and Applied Sciences, Universitas Syiah Kuala, Banda Aceh, Indonesia
[5]Biology Education, Faculty of Teacher Training and Education, University of Lampung, Lampung, Indonesia

Author correspondency*:
mohamad.amin.fmipa@um.ac.id

Abstract

Inflammation is a tissue injury that occurs due to physical trauma or microbiological substances that involve the activities of many cell types. Inflammation can be prevented using the natural medicines from *Allium cepa* L. Quercetin is one of the bioactive compounds found in *Allium cepa* L and has been reported to have anti-inflammatory activity. The natural medicines have been used to minimize non-steroidal anti-inflammatory drugs. This study aims to investigate the modeling structures and the protein receptor from quecertin in inflammation mechanism and their optimization of the effectiveness in the human body. The bioinformatics tools used in this study are the database of quercetin compounds, Pubchem and Swis Target Prediction protein prediction databases, PyRx 0.8 molecular docking software, ligand docking, and binding site analysis with PyMOL and LigPlus software. The results from in silico show that quercetin compounds can interact with Muscleblind-like protein 1 target protein with a Binding Affinity minus value which is not much different from the dexamethasone compound. Dexamethason is a standart because it is a corticosteroid drug that can be used as an anti-inflammatory to reduce inflammation, allergic reactions, arthritis and other inflammatory diseases.

Keywords: *Allium cepa* L.; anti inflamation; in silico, quercetin

INTRODUCTION

Quercetin compounds are found in the *Allium cepa* L. that contain compounds including carbohydrates (11.0 g), protein (1.2 g), fiber (0.6 g), fat (0.30%) and several vitamins such as vitamin A (0.012 mg), vitamin C (11 mg), thiamin (0.08 mg), riboflavin (0.01 mg), and niacin (0.2 mg), and some minerals such as phosphorus, calcium, sodium, iron and potassium (Rodrigues et al., 2003). Quercetin has a molar mass of 302,236 g/mol, in the form of yellow crystalline powder, a density of 1,799 g/cm3 and a melting point of 316 ° C (Smith et al., 2003).

Inflammation is a local reaction to tissue infection or injury and involves more mediators. Inflammation has a fairly high incidence, where inflammation can be caused by physical trauma, infection or antigenic reactions from an illness. The natural secondary metabolite compound that has the potential for inflammatory treatment is Quercetin, which is abundant in the *Allium cepa*. Chronic inflammation means long-term inflammation, which can last for several months and even years. This is due to the failure to remove anything that causes acute inflammation, an autoimmune response to self-antigens (the immune system attacks healthy tissue), an existing low-intensity chronic irritation.

The research on *Allium cepa* has been done before, however the mechanism of quercetin compounds can prevent the occurrence of inflammatory processes is unknown. Therefore, this study aims to identify natural bioactive compounds from onion *Allium cepa* for anti-inflammatory based on in silico. We investigate the modeling structures and the protein receptor from quercetin in inflammation mechanism and their optimization of the effectiveness in the human body.

MATERIALS AND METHODS

In silico screening in this research was conducted following the previous methods (Maulina, *et. al.*, 2018; Pangastuti *et.al*, 2016; 2018 and Ilmawati, 2017).

Retrieval of sample

This research used the spesific compound from *Allium cepa* L. The quecertin is the most abundant compound in *Allium cepa* L (Fredotović, Z. et al., 2017) and it has been reported to have anti-inflammatory activity. Therefore, quecertin was selected as a specific sample for analysis. In addition, the compositions of quercetin were obtained from the compounds database of PubChem.

Preparation of ligand

The structure of Quercetin 3D chemical compounds and SMILES ligands is taken from the database on the pubcem server online (https://pubchem.ncbi.nlm.nih.gov/) with ID number: CID: 5280804.

Target Selection

Target protein selection is predicted by using the help of a number of servers to check and ensure the target protein is selected correctly. First, enter the ligand Quercetin SMILES value on the Pharmmapper server online (http://59.78.96.61/pharmmapper/) to identify potential target proteins. Second, observing potential target proteins on the Swiss Target Prediction server online (http://www.swisstargetprediction.ch/) to look for similar target proteins which found on the first server. Third, observing potential target proteins on the SuperPret server online (http://prediction.charite.de/) to adjust the similarity of target proteins which found on the first and second servers. The process of observing the target protein is carried out repeatedly to ensure the similarity of the target protein is correct, so could be not to affect the failure or inaccuracy during the docking process.

Docking Molecules

Docking of quercetin molecules, target proteins, and control compounds (dexamethasone) which are chemical drugs in the treatment of inflammation using PyRx 0.8 software.

Visualization and Molecular Interaction

The interaction between quercetin, target proteins, and control compounds known based on protein visualization was then analyzed using PyMol and LigPlus software and Discovery Studio 2016 Client.

RESULTS AND DISCUSSION

Target selection results using Pharmmapper (JOB ID: CID 5280804), Swiss Target Prediction and SuperPret found that quercetin interacts with the Muscleblind-like protein 1 receptor. Quercetin is a group of flavonoids produced by plants and can be used to treat inflammatory diseases and these compounds can be isolated from bulb onions (*Allium cepa*). Based on the results of the study it was found that quercetin compounds were able to bind to muscleblind-like protein 1 receptor protein (Fig. 1) by forming bonds at one end of the side. Visualization results using PyMol and LigPlus software show the following images (Figure 1).

The bonding between muscleblind-like protein 1 receptor as a target protein and quercetin compound has the same position as chemical compounds which have generally been used as inflammatory drugs, namely dexamethasone (Figure. 2).

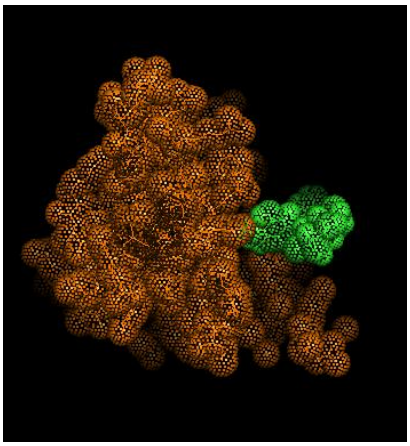

Figure 1. Binding visualization between protein target (muscleblind-like protein 1 receptor) and natural bioactive quercetin (brown is protein target; green is quercetin).

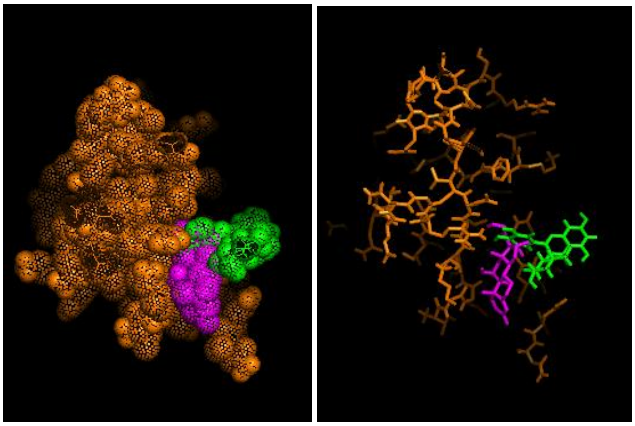

Figure 2. Visualization of binding between protein target, quercetin as bioactive compound and dexamethasone as control compound. Note: brown color for protein target; green for quercetin and purple for dexamethason).

Dexamethasone is a corticosteroid drug that can be used as an anti-inflammatory to reduce inflammation, allergic reactions, arthritis and other rheumatic diseases, skin diseases, intestinal diseases such as ulcerative colitis and multiple sclerosis or myasthenia gravis. In general, Dexamethasone is widely used in the therapy of chronic inflammatory diseases for its pain-modulating effects (Laste et al, 2013). Moreover, dexamethasone significantly inhibited the levels of TNF-α and IL-6, suggesting a key role for these cytokines in sickness behavior (Plessers et al. 2015).

The results showed in Figure 2 indicate that the natural compound of quercetin has the same molecular interaction as dexamethasone, a chemical compound that is often used as an anti-inflammatory drug. In addition, the results of the interaction analysis of the natural compound quercetin and the Muscleblind like protein 1 protein were compared with the dexamethason**e**

chemical compound with the Muscleblind like protein 1 protein, which showed no significant difference. This shows that the natural compound quercetin is very potential to be used as an anti-inflammatory drug. The results of the calculation analysis of the target protein ligand bond interaction is described in Table 1 and 2 as following.

Table 1. The analysis of the interaction of quercetin compounds with muscleblind-like protein 1 target protein.

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
Quercetin- Muscleblind-like protein 1	-6.5	0	0
Quercetin- Muscleblind-like protein 1	-6.3	21.774	17.9
Quercetin- Muscleblind-like protein 1	-6.1	4.053	2.596
Quercetin- Muscleblind-like protein 1	-6	8.163	4.193
Quercetin- Muscleblind-like protein 1	-5.8	22.599	18.725
Quercetin- Muscleblind-like protein 1	-5.8	22.149	18.221
Quercetin- Muscleblind-like protein 1	-5.8	22.272	19.67
Quercetin- Muscleblind-like protein 1	-5.7	6.343	1.724
Quercetin- Muscleblind-like protein 1	-5.7	4.238	2.877

Table 2. The analysis of the interaction of dexamethasone compounds with muscleblind-like protein 1 target protein.

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
Dexamethasone - Muscleblind like protein 1	-6.5	0	0
Dexamethasone - Muscleblind like protein 1	-6.2	3.953	2.41
Dexamethasone - Muscleblind like protein 1	-6	7.669	2.149
Dexamethasone - Muscleblind like protein 1	-5.8	21.751	19.441
Dexamethasone - Muscleblind like protein 1	-5.8	7.481	1.846
Dexamethasone - Muscleblind like protein 1	-5.7	25.176	23.523
Dexamethasone - Muscleblind like protein 1	-5.7	21.778	19.947
Dexamethasone - Muscleblind like protein 1	-5.7	16.298	13.067
Dexamethasone - Muscleblind like protein 1	-5.7	19.714	16.467

Analysis based on data in Tables 1 and 2 shows that it is not significantly different from the chemical bonds between quercetin and dexamethasone, with the binding affinity value of the two compounds in the similar ranges. The binding affinity value shows the best bond between the ligand and the target protein. The minus value shows that the ligand is easier to bind to the target protein because it requires less energy to bind. Based on the range of binding affinity values showed that many ligand residues that bind to the target protein, especially in dexamethasone compounds as control compounds have better bond range than natural compounds, quercetin compounds. But from the range of values these two compounds show not much different. Visualization of the results of inter-molecular interactions using the Discovery Studio 2016 Client software shows that the bond distance between molecules and the type of bond that occurs on each residues of the ligand molecule and target protein more details show in Figure 3 and 4.

Cyclooxygenase (COX) or prostate glandinendo peroxide synthase (PGHS) is a bifunctional enzyme that initially converts arachidonic acid to prostaglandin G2 (PGG2) through oxygenated, then catalyzes PGG2 peroxidase to PGH2. PGH2 is a precursor to the formation of several important mediators for pain, fever and inflammation. Two forms of cyclooxygenase enzyme isoforms are known, namely COX-1 and COX-2. COX-1 is a constitutive enzyme that have a role for play in the regulation of several cellular processes, including homeostasis vascular, protection of the gastrointestinal tract and kidney function. COX-2 is induced and is in inflamed tissue. Inhibition of this COX enzyme is the main working mechanism of non-steroidal anti-inflammatory drugs that are widely used (Kartasasmita et al, 2009).

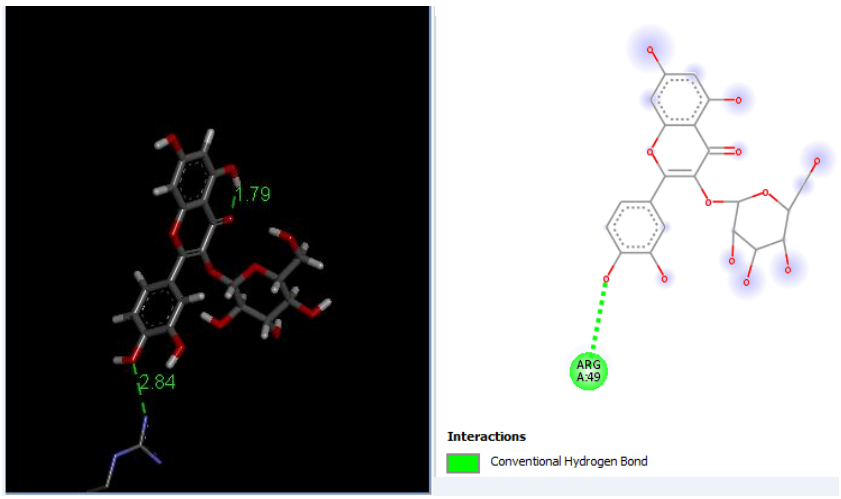

Figure 3. Distance of intra interaction between quercetin (bioactive compound) and protein target (Muscleblind-like protein 1) and the type of binding.

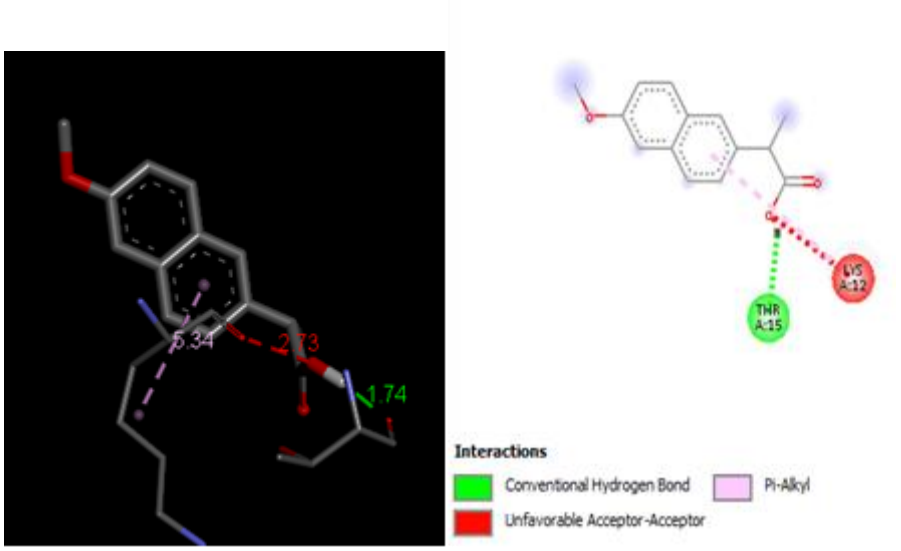

Figure 4. Distance of intra interaction between dexamethasone (control compound) and protein target (Muscleblind-like protein 1) and the type of binding.

Cyclooxygenase (COX) or prostate glandinendo peroxide synthase (PGHS) is a bifunctional enzyme that initially converts arachidonic acid to prostaglandin G2 (PGG2) through oxygenated, then catalyzes PGG2 peroxidase to PGH2. PGH2 is a precursor to the formation of several important mediators for pain, fever and inflammation. Two forms of cyclooxygenase enzyme isoforms are known, namely COX-1 and COX-2. COX-1 is a constitutive enzyme that have a role for play in the regulation of several cellular processes, including homeostasis vascular, protection of the gastrointestinal tract and kidney function. COX-2 is induced and is in inflamed tissue. Inhibition of this COX enzyme is the main working mechanism of non-steroidal anti-inflammatory drugs that are widely used (Kartasasmita et al, 2009).

CONCLUSION

This study proves that the natural compound quercetin found in onion plants (*Allium cepa* L) has the potential as an anti-inflammatory drug. The type of chemical bounding between protein ligand and control compound (dexamethasone) is similiar. There is no to significant the bond distance and type of chemical bond formed.

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