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Molecular Docking Analysis of Quercetin and Diclofenac as Cox-2 Potential Inhibitors

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Abstract

Currently, many herbal medicines are being researched to accelerate the healing of tooth extraction wounds. Natural herbal medicines generally contain flavonoids to treat inflammation of the wound, which is a product of plant metabolism that has many phenolic structures. One type of flavonoid that is known to be able to play a role in overcoming inflammation in tooth extraction wounds is quercetin. Nowadays, there has been found many anti-inflammatory compounds from natural materials. However, there are no known chemical compounds, which is selectively inhibit COX-2. The purpose of this paper is to predict the mechanism of action of anti-inflammatory compounds from natural substances at the molecular level, as COX-2 inhibitors using the Molecular Docking Simulation method.

The target or receptor compound is cyclooxygenase-2 (COX-2). Before the docking is done, the target compound must be prepared beforehand. The compound that has been downloaded from the RCSB PDB is displayed in the window through I PXX code, the water compounds and the co-factor should be removed so that can be ensured that the action is the test compound and the target compound. Docking done by native ligand on the receptor. Native ligands are prepared as well as on the above test preparation compounds.

The calculation results of the natural compound quercetin that can bind COX-2 are indicated by energy and hydrogen bond interactions (ΔG). The results showed that the best hydrogen bond (ΔG) was quercetin compound which was characterized by the presence of 5 hydrogen bonds compared to diclofenac which only 2 hydrogen bonds occurred with the residues in the binding site. The rerank score also shows that the energy required for quercetin to interact with the COX-2 receptor is also smaller at -98.9 when compared to diclofenac which is -88.7

Quercetin compounds are predicted to have better in silico activity against COX-2 inhibition than diclofenac.

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Introduction

Antipyretic analgesic drugs and non-steroidal anti-inflammatory drugs (NSAID) is one of many drugs prescribed by doctors. These drugs have many similarities in therapeutic effects as well as the side effects.[1]

The NSAID drug class inhibits cyclooxygenase enzymes so that the conversion of arachidonic acid into PGG2 is impaired. Each NSAID drug inhibits cyclooxygenase with different strength and selectivity. The NSAID group include diclofenac, parecoxib, celecoxib, and etoricoxib.[2]

Cyclooxygenase are enzymes that catalyze the formation of prostaglandins, an inflammatory mediator, and arachidonic acid metabolism products. The COX-I enzyme is constitutive for maintaining normal physiology and homeostasis, whereas COX-2 is an enzyme induced in inflammatory cells by cytokines, endotoxins, and growth factors. COX-2 also plays a role in the proliferation of cancer cells. Excessive expression of COX-2 found in most tumors. As we know that the role of COX-2 in the inflammatory process, it is necessary to search for the NSAID drug bonds corresponding to the

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receptor that binds to the COX-2 enzyme. Therefore, it is necessary to study the compounds that can inhibit COX-2, which is can be done more easily with the computational technology. A computational study known as terminology *in silico* is an *in vivo* and *in vitro* analogue, which uses computer applications so that time and cost become more efficient.[3,4]

Terminology *in silico* known as the virtual analyzed screening. It is very difficult to do biological chemical compound structure screen against billions of its, hence a virtual approach becomes an alternative choice. To do with this method was relatively faster to handle thousands or millions chemical compounds in a few day and depends on the compounds tested and the speed of the computer used. Nowadays, the used of technology virtual screening has achieved a good status as a modern and economic advantage technology in the invention of chemical drug compounds.[5]

The process of virtual screening used to help discovering potentially compounds that can be used as drugs, which is requiring relatively short periods. If the target is known already, the docking algorithm can be used to place the drug candidate into the active side of the target such as enzyme or receptor. Then the interactions of the bonded chemical compounds are sequenced according to computational analysis of the electrostatic components and the steric.[6]

Nowadays, there has been found many anti-inflammatory compounds from natural materials. However, there are no known compounds, which selectively inhibit COX-2.

Based on the above description, there is a composition which is specifically modeled the interactions of some known compounds known to have anti-inflammatory activity through COX-2 inhibition.

The method used in this study is an interaction study of several natural material compounds known to inhibit COX-2 by using computer applications *in Silico* at the molecular level or known as Molecular Docking Simulation method using some informations from the target structure as well as the physicochemical properties of the ligand that may be screened by interaction tests of compounds known to inhibit COX-2 on the active side.[7]

The purpose of this paper is to predict the mechanism of action of anti-inflammatory compounds from natural substances at the molecular level, as COX-2 inhibitors using the Molecular Docking Simulation method.

The benefit of this paper is to show the interaction of anti-inflammatory compounds from natural substances that are known selectively inhibit COX-2, so that the mechanism of action of the compounds can be predicted as a COX-2 inhibitor at the molecular level.

In this study, we studied the interaction of anti-inflammatory compounds group from a class of compounds that had been isolated and identified by previous researchers of various references.

Materials and methods

The method used in studying such interactions is molecular docking. Docking is a method in which another compound and at the same time calculate the interaction energy of the same orientation from both compounds. A docking procedure is used as a reference to determine the proper orientation of the compound that are relatively against other compounds.

The target or receptor compound is cyclooxygenase-2 (COX-2). Before the docking is done, the target compound must be prepared beforehand. The compound that has been downloaded from the *RCSB PDB* is displayed in the window through I PXX code, the water compounds and the co-factor should be removed so that can be ensured that the action is the test compound and the target compound.[8,9]

Docking (re-docking) done by docking native ligand on the receptor. Native ligands are prepared as well as on the above test preparation compounds.

Results

The calculation results of the natural compound quercetin that can bind COX-2 are indicated by energy and hydrogen bond interactions (ΔG).

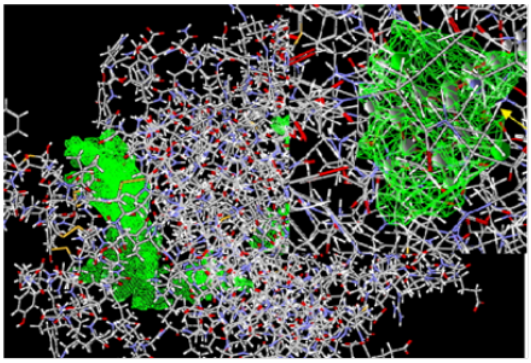

Figure 1. Holes in 1PXX receptors where drugs interact (cavity 4, vol=79.36).

Figure 2. Quercetin and diclofenac in cavity 4 in the image of the secondary structure of the protein.

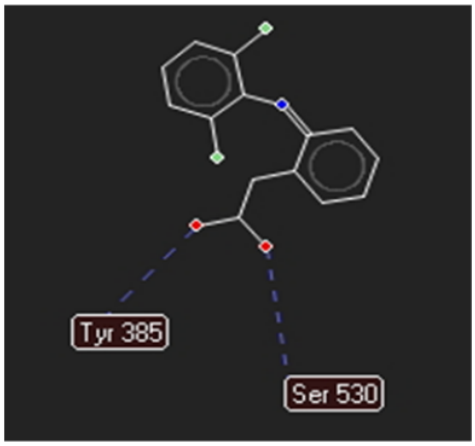

Figure 3. 2-D picture of the interaction process between diclofenac and COX-2 receptors (1 PXX).

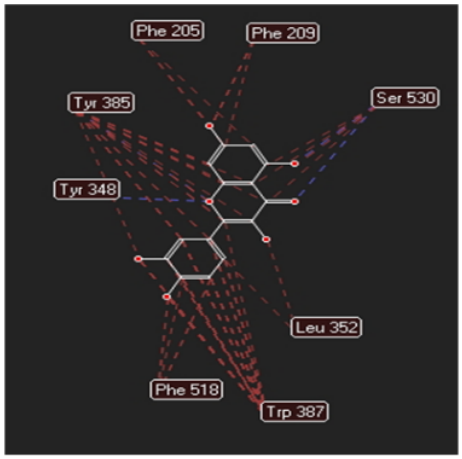

Figure 4. 2-D picture of the steric process of interaction between quercetin and COX-2 receptors (1 PXX).

Discussion

In dentistry, tooth extraction wounds take a long time to heal. Currently, many herbal medicines are being researched to accelerate the healing of tooth extraction wounds. Natural herbal medicines generally contain flavonoids to treat inflammation of the wound, which is a product of plant metabolism that has many phenolic structures. Flavonoids are also useful as anti-inflammatory and improve blood circulation. One type of flavonoid that is known to be able to play a role in overcoming inflammation in tooth extraction wounds is quercetin. Inflammation is caused at the beginning of the injury. The healing process then occurs in this defect tissue is healing which could be divided into four phases, namely hemostasis, inflammation around the wounds, proliferation cells, and tissue remodeling phases. Wounds that caused by tooth extraction, always includes the soft tissues and hard tissues. The drugs commonly used by dentists today are anti-inflammatory which play a role in inhibiting COX 2 or COX 2 inhibitors. COX 2 inhibitors are non-steroidal anti-inflammatory drugs or NSAIDs that work more specifically to inhibit the COX 2 enzyme.[9-11]

In this in silico study, the comparison of quercetin as an anti-inflammatory from natural ingredients, showed a better effect in inhibiting COX2 than diclofenac. Docking modeling starts with the holes in 1PXX receptors where drugs interact (figure 1), then quercetin and diclofenac

showed in cavity in the image of the secondary structure of the protein (figure 2).

The calculation results of the natural compound quercetin that can bind COX-2 are indicated by energy and hydrogen bond interactions (ΔG). The results showed that the best hydrogen bond (ΔG) was quercetin compound which was characterized by the presence of 5 hydrogen bonds compared to diclofenac which only 2 hydrogen bonds occurred with the residues in the binding site. The rerank score also shows that the energy required for quercetin to interact with the COX-2 receptor is also smaller at -98.9 when compared to diclofenac which is -88.7 (figure 3 & 4)

Conclusions

Quercetin compounds are predicted to have better *in silico* activity against COX-2 inhibition than diclofenac.

Acknowledgments

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Declaration of Interest

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