KnE Medicine

ICMEDH
The International Conference of Medicine and Health (ICMEDH)
Volume 2022

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Conference Paper

# Anticancer Activity of in Silico Interaction Between Curcumin and Cyclooxygenase 2 Enzyme

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**Abstract.**
In this research, the in silico interaction between curcumin and cyclooxygenase 2 (COX-2) was investigated using molecular docking with the AutoDock 4.0 software application. This study aimed to determine the pharmacokinetic profile of the compound, affinity, and exchange of curcumin with COX-2 inhibitors in silico. Curcumin's interactions with COX-2 were compared to those of the known COX-inhibitor, celecoxib. The pharmacodynamic test was used to show the free bond energy. Curcumin demonstrated anticancer activity by inhibiting the metabolism of arachidonic acid through the enzyme COX-2 and inhibiting free radicals in the enzymatic pathway. This was indicated by the value free energy (ΔG) of the curcumin compounds having a binding energy value of -8.81 kcal/mol, which is smaller than that of arachidonic acid (-5.20 kcal/mol). However, celecoxib had a more stable bond with the COX-2 inhibitors than curcumin, with a value of -10.11 kcal/mol. As a result, curcumin can be considered a suitable lead compound in developing new COX-2 inhibitors, which are a potential target for anticancer drugs.

**Keywords:** curcumin, COX-2 inhibitor, anticancer

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**Published** 15 September 2022

Publishing services provided by Knowledge E



Selection and Peer-review under the responsibility of the ICMEDH Conference Committee.



## 1. Introduction

IARC data 2020 (International Agency for Research on Cancer) breast cancer ranked first in the cause of death by 9.6%, followed by cervical cancer at 9.0%. The most successful therapies for localized and non-metastatic cancers are surgery and radiotherapy, but they are ineffective if cancer spreads throughout the body. Cancer treatments (chemotherapy, hormone, and biologic therapy) can reach any organ in the body infected by cancer cells through the bloodstream[1] . Because of this, it is necessary to find new treatments that selectively kill cancer cells without affecting normal cells. Indonesia is the second-largest country in the world, with abundant biodiversity, including medicinal plants. This plant is used as a colorant and seasoning in daily cooking in

Indonesia. Besides that, it is also used as medicine [2]. Curcumin (1,7–bis– (4–hydroxy–3–methoxyphenyl)1,6–heptadiene–3,5– dione, is a compound isolated from the plant Curcuma sp.

Curcumin has several modes of action in its anticancer activity, including antioxidant and radical scavenging activity, which indicates its role as an inhibitor of cancer carcinogenesis (Nurrochmad, 2004). According to the study, Curcumin is also active in suppressing cancer cell multiplication in vivo and in vitro when administered early and metastatic phases [3]. Supported in research [4], Curcumin has the effect of promoting the process of apoptosis, which is a natural mechanism of cell death. Curcumin has also been shown to prevent the growth of human breast cancer cells without affecting estrogen receptors. Celecoxib is currently being developed into an anticancer drug that acts on COX-2 inhibitors. However, there has been no study comparing Curcumin's anticancer activity affecting COX-2 inhibitors compared to celecoxib. This study aimed to determine the pharmacokinetic profile of the compound, affinity, and exchange of Curcumin with Cyclooxygenase 2 (COX-2) inhibitors by in silico method.

## 2. Methods

Pharmacodynamic testing begins with determining the target protein, and the criteria must include the target protein to be used in homo sapiens. It is because the target protein to be studied is drug interactions in humans. The selection of the target protein must be complete with ligands because the molecular docking process can only be done with drugs that have ligands. The docking method is said to be valid if the RMSD value is 2Å. In table 3, the table of the results of the docking method validation shows a lot of RMSD 2Å. It indicates that the docking method is valid. The final result of the docking process is the RMSD value, the number of clusters, the Inhibition Constant value, and the binding energy. The prediction of ligand interaction activity with the target protein is in the form of binding energy.

The databases used to predict pharmacokinetics are PubChem, Protein Data Bank, and SwissADME. The structure of plant chemical compounds accessed on PubChem in 2D and 3D. The secondary metabolites obtained from the dr. Duke website and the target protein obtained from the Protein Data Bank. SMILES inputted into PubChem is a chemical notation designed by computer experts that can interpret a chemical structure accurately and precisely with the help of a computer. The results are Druglikeness and Boiled Egg data to conclude secondary metabolite compounds with good bioavailability.

The software used for pharmacodynamic profile prediction is Autodock 4.0 docking software, PyRx 0.8 series for docking compounds or drugs, Discovery Studio to separate the contents of the PDB file and visualize the final results in 3D, which, for 2D visualization, is done using a webserver. Protein. Plus. The docking simulation results carried out 100 times have 100 docking poses that have their respective bond energies. The bond energy taken is the most negative because it has a strong interaction.

## 3. Result and Discussion

In this study, 72 compounds found which predicted to have good bioavailability. Drug-likeness is a qualitative concept used to describe the similarity of a compound as a drug candidate. Drug likeness evaluated by the Lipinski Rule of Five discusses four simple physicochemical parameters (molecular weight 500, log P≤ 5, hydrogen bond donor ≤ 5, hydrogen bond acceptor ≤10) associated with 90% of orally active drugs that have passed the drug status. The free bond energy describes the stability and spontaneity of the binding between the ligands and the target protein. The lower the value of G, the more stable and spontaneous bonds will be. The inhibition constant (IC) is a value that describes the affinity between the compound and its decomposition. The smaller the IC value, the greater the affinity of the ligand to the receptor.

The bond energy taken is the most negative because it has a strong interaction. Due to the presence of polar functional groups on the ligands such as methyl (-CH3), hydroxyl (-OH), and amine (-NH3). Arachidonic acid metabolism is thought to play a critical role in the occurrence of carcinogenesis. This metabolic pathway is associated with the formation of prostanoids. Prostanoids belong to the subclass of eicosanoids converted into prostaglandins, thromboxane, and prostacyclin [5]. Cyclooxygenase-2 (COX-2) is a critical enzyme in converting arachidonic acid to prostaglandins, first identified 20 years ago. Several studies have suggested the involvement of prostanoids in the pathogenesis of cancer.

Table 1: Positive Control Docking Results vs. curcumin and celecoxib against Cyclooxygenase-2 (COX-2).

| No | Code | Compounds | Cluster | The Number of Poses in The Largest Cluster | Energy Binding Prediction (kcal/mol) | Prediction constant of inhibition |
|---|---|---|---|---|---|---|
| **1** | mol 40 | Curcumin | 5 | 37 | -8,81 | 348,48 nM |
| **2** | Ligand | Celecoxib | 1 | 100 | -10,11 | 28,73 nM |

Curcumin reported showing anti-cancer activity by inhibiting arachidonic acid metabolism through the enzyme Cyclooxsigenase-2 (COX-2) and inhibiting free radicals in the

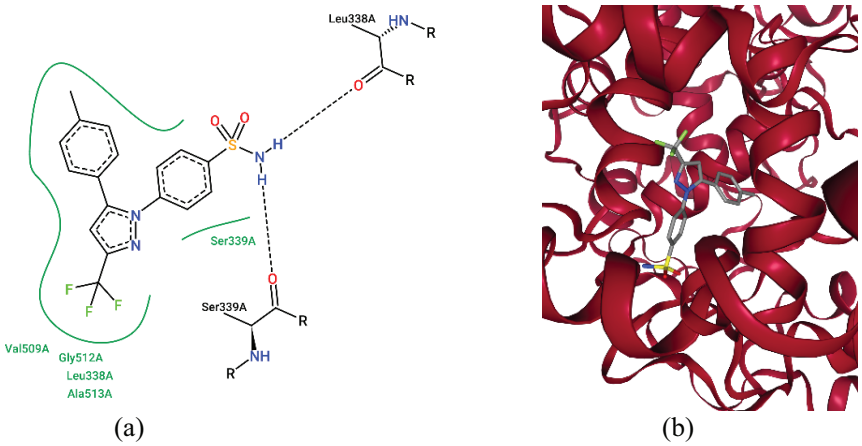
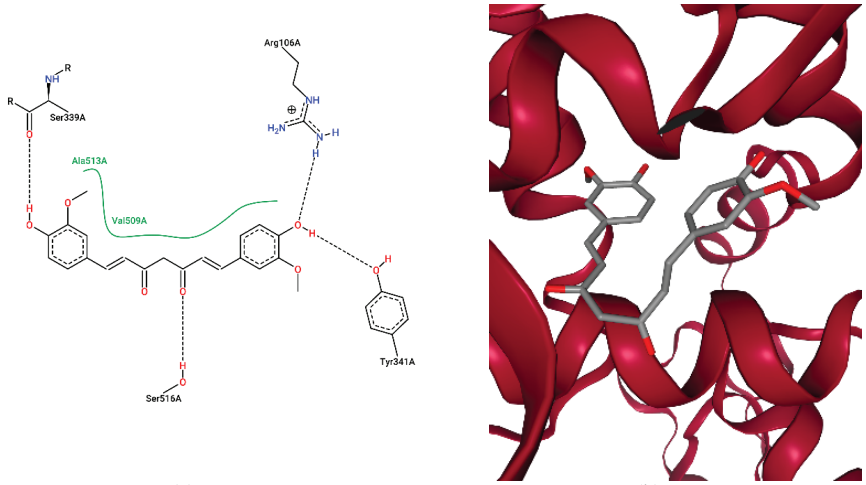



**Figure** 1: Forms of Interaction Between Positive Control and Curcumin Against Cyclooxsigenase-2 (COX-2) Enzyme.

enzymatic pathway. It is indicated by the value (ΔG) of the curcumin compound, which has a binding energy value of -8.81 kcal/mol nM, smaller than arachidonic acid (-5.20 kcal/mol). Arachidonic acid will produce prostaglandins due to enzymatic reactions by the Cyclooxygenase-2 (COX-2) enzyme to trigger cancer if there is an overexpression of the enzyme. However, the delta G value of celecoxib was lower (-10.11 kcal/mol) than curcumin. It indicates that celecoxib is more stable with the enzyme cyclooxygenase-2 (cox-2) compared to curcumin. Chemical bonds other than hydrogen bonds can occur due to flexible ligands interacting with receptors. Interactions can be in the form of non-covalent or non-bonded interactions, which occur between the ligand and the receptor, increasing the affinity of the ligand to the receptor.

Observation of residue contacts aims to determine interactions other than hydrogen bonds between the ligand and the target protein. The residue that makes contact with the ligand has a non-binding interaction between the ligand and the target protein, which will increase the affinity and inhibitory activity of the Cyclooxygenase-2 (COX-2) enzyme. Curcumin has 3 of 7 amino acid residues similar to celecoxib, namely Ser 339A, Val509A, Ala 513A.

The mechanism of action of curcumin as an anticancer shows its active role in inhibiting carcinogenesis at the initiation and promotion or progression stages. In addition, curcumin can inhibit cell proliferation and induce cell cycle changes in the colon adenocarcinoma cell line without depending on the prostaglandin pathway. COX-2 expression in cancer plays a role in various carcinogenesis processes such as increasing




(a) (b)

**Figure** 2: Forms of Interaction Between Positive Control and Celecoxib Against Cyclooxsigenase-2 (COX-2) Enzyme.

cell proliferation, suppressing apoptosis, increasing invasion ability, and metastatic capacity.

## 4. Conclusion

This study found that the compound curcumin has a good affinity, which showed from the best Free energi and Constanta Inhibition value, and has a similar bond with the Celecoxib ligand. Curcumin has potential as an anti-cancer

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