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Cox2 Inhibitor Test Of Limpasu (Baccaurea Lanceolata) Using Computation Method

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ABSTRACT

The use of anti-inflammatory drugs with the COX-2 method is starting to develop tolerance, so that drugs circulating in the community now cause various kinds of complaints, namely inhibition of blood clotting and stomach ulcers. Therefore, the purpose of this study was to screen natural product compounds that have potential as COX-2 inhibitors. The materials used are compounds contained in B.lanceolata and COX-2 enzymes with code 3ln1 obtained from the RCSB database, the equipment used is a windows laptop with PLANT and discover studio software, the method used in this study is a computational study using docking software . The results in this study were that the docking score of B. lanceolata was higher than the native ligand, so the effectiveness was weaker than the native ligand, the docking scores obtained were as follows: Epidihydrotutin (-50.243); Sapidolide A (-51052); Melatonin (-53039); 6'-O-Vanilloylisotachioside (-60.910) and 6'-O-Vanilloyltachioside (-61.131). In conclusion, 6'-O-Vanilloyltachioside is a potential compound as a COX-2 inhibitor from B.lanceolata.

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1. Introduction

Currently, the deficiencies in the development of new drugs have begun to be overcome through a drug discovery approach using computational methods. This method is part of the field of chemistry which involves the application of chemical theory to develop computer programs that can calculate the properties and changes of molecules (Alrumaihi, 2021) . In addition, this approach also involves simulating large systems such as macromolecules (such as proteins and nucleic acids) as well as complex systems. Using this technique, we can study the conformation of molecules and their changes, for example in the process of protein denaturation, as well as phase changes (Allison, 2020) . This computational approach also allows us to estimate macroscopic properties such as specific heat based on the behavior of atoms and molecules (Kulik et al., 2012) .

Theoretical chemistry refers to mathematical explanations in chemistry, while computational chemistry is used when mathematical methods have developed well enough to be applied in computer programs (X. Wang et al., 2018) . Computational chemical methods have the potential to make

predictions, although they cannot always be applied directly because many aspects of chemistry are difficult to calculate with precision. Almost all aspects of chemistry can be explained through a computational approach both qualitatively and quantitatively. A number of methods, such as PLANTS, Autodock 4.2 (Weni et al., 2020) , Biovia, Autodock Vina, and others, have been used in computational chemistry applications.

Inflammation is a protective response of body tissues that occurs due to tissue injury or damage, which aims to overcome, reduce, or limit the agent causing the injury or damage. (Zhang et al., 2022) . This process involves eliminating or reducing the causative agents of the problem as well as repairing damaged tissue. When inflammation occurs, symptoms that appear include red skin (rubor), burning sensation (calor), pain (dolor), swelling (tumor), impaired function (functio laesa), and an increase in the number of neutrophil cells in the area of the body that is experiencing inflammation (Xiang et al., 2022) .

Inflammation is one of the foundations of various diseases due to its exaggerated response to stimuli, including Osteoarthritis (OA) and asthma (MacDonald et al., 2017) . One type of anti-inflammatory drug that is widely used in the treatment of cases associated with inflammation is non-steroidal anti-inflammatory drugs (NSAIDs). However, the use of NSAIDs should be avoided in patients who have a history of gastritis or peptic ulcers, as well as in patients with blood clotting disorders such as hemophilia (Patil et al., 2019) . The use of NSAIDs that inhibit cyclooxygenase (COX) enzymes is not recommended in the long term because they can cause peptic ulcers, nephropathy due to analgesics, inhibition of blood clotting function, inhibition of labor, and an increased risk of hypertension (Bacchi et al., 2012) . Therefore, it is necessary to search for other compounds that have potential as COX inhibitors. One of the potential plants is spleen, which has the Latin name Baccaurea lanceolata.

Baccaurea has activity as an anti-inflammatory (Ahmed et al., 2015) . Baccaurea also has analgesic and anti-inflammatory activity in vitro (Nesa et al., 2018) . Baccaurea also has the antibacterial activity of Streptococcus sanguis (Norhayati et al., 2019) . Activities in overcoming the development of Escherichia coli and Bacillus cereus have been carried out (Zamzani & Triadisti, 2020) . Based on the above analysis, it is necessary to screen compounds that have the potential as COX-2 inhibitors.

2. Methods

Materials and Equipment

In the framework of this study, the materials used involved the COX-2 protein taken from PDBhttps://www.rcsb.org with the identification code 3ln1, and the *B.lanceolata compound* obtained from KNAPSack. The software used in this experiment was a computer running Windows 10, as well as programs such as PLANTS and Biovia Discovery Studio.

Pre-preparation of COX-2 Protein

The first step involves downloading the COX-2 protein coded 3ln1 from the PDB website https://www.rcsb.org. Furthermore, compounds from B. lanceolata were retrieved from the KNAPsack database (Nakamura et al., 2013) and prepared with chemaxon (ChemAxon, 2016) . This process was followed by preparing COX-2 proteins and isolating native ligands using the Yasara software (Krieger & Vriend, 2014) . This is done to create a space or cavity (pocket/cavity) to be used in the docking process, so that the structure and coordinates of this cavity can be known before docking.

Docking

Docking of the ligand to the receptor was carried out using PLANTS (Korb et al., 2009) . The binding pocket on the COX-2 protein, where the ligand will bind, is shaped and considered so that it includes all the amino acid residues involved in the interaction between the ligand and COX-2. After that, a grid box is formed with a size that matches the dimensions of the protein to cover the entire structure. This grid is placed at the location where the ligands will bind. The docking process is carried out in various grid dimensions using the ANT Algorithm on the PLANTS device. This process is carried out through commands in the command prompt, and the results of the docking are stored in the *mol2 file format.

Docking Results Visualization

The interaction between the ligand and the receptor was visualized using the Biovia Discovery Studio software (Biovia, 2020) .

Analysis of Docking Simulation Results

Evaluation of the docking results involves a number of parameters, such as the orientation of the ligand structure, hydrophobic interactions, the formation of hydrogen bonds, as well as the value of the free energy resulting from the docking process of the ligand molecules.

3. Results and Discussion

The COX-2 protein identified by the code pdb 3LN1 is a COX-2 enzyme which has an isoenzyme form with a chain length of 587 amino acids (JL Wang et al., 2010) . The COX-2 enzyme contains four different oligosaccharide structures, one of which plays a role in the process of protein folding, and the fourth oligosaccharide structure plays a role in the degradation of this protein. The gene responsible for COX-2 production, called Ptgs-2, is activated especially when there is stimulation from inflammatory mediators or bacterial endotoxins in tissues. When this gene is activated, a 4 kb long mRNA molecule is produced which tends to be easily damaged due to its instability in the 3'-untranslated region (Mayne et al., 2012) . So we need screening that is capable of inhibiting COX-2. Compounds from B.lanceolata that have anti-inflammatory abilities can be seen in **Table 1** and The docking coordinates are X:30.9886 ; Y:-22.2836, Z :-16.5072 and radius : 11.1017.

Table 1 .
Activity score prediction

Name	Mark	
	Pa	Pi
Melatonin	0.256	0.162
Epidihydrotutin	0.546	0.044
Sapidolide A	0.404	0.099
6'-O-Vanilloylisotachioside	0.563	0.040
6'-O-Vanilloyltachioside	0.662	0.021

Table 2 .
Docking scores and interactions

Name	dock score	interacting residue
ligand native (4-[5-(4-METHYLPHENYL)-3-(TRIFLUOROMETHYL)-1H-PYRAZOL-1-YL]BENZENESULFONAMIDE)	-79,522	HIS75; GLN178; TYR334; VAL335; LEU338; SER339; TYR341; LEU345; PHE367; LEU370; TYR371; TRP373; ARG499; ALA502; ILE503; PHE504; MET508; VAL509; GLY512; ALA513 SER516; LEU517
Melatonin	-53,039	HIS75; GLN178; TYR334; VAL335; LEU338; SER339; TYR341; PHE367; LEU370; TYR371; TRP373; ARG499; ALA502; ILE503; PHE504; MET508 ; VAL509; GLY512; ALA513; SER 516
Epidihydrotutin	-50,243	TYR334; VAL335; LEU338; SER339; TYR341; PHE367; LEU370; TYR371; TRP373; PHE504; MET508; VAL509; GLY512; ALA513; SER 516
Sapidolide A	-51,052	MET99; VAL102; LEU103; ARG106; ILE331, VAL335; SER339; TYR341; LEU345; ALA513; PRO514; SER516; LEU517
6'-O-Vanilloylisotachioside	-60,910	LEU78; MET99; VAL102; ARG106; PHE191; VAL330; ILE331; TYR334; VAL335; LEU338; SER339; TYR341; LEU345; TYR371; TRP373; ILE503; PHE504; MET508; VAL509; GLY512 ALA513; SER516; LEU517; LEU520
6'-O-Vanilloyltachioside	-61,131	VAL74; LEU78; MET99; VAL102; SER105; ARG106; VAL330; ILE 331; TYR334; VAL335; LEU338; SER339; TYR341; LEU345; LEU370; TYR371; TRP373; PHE504; MET508; VAL509; GLY512; ALA513; PRO514; SER516; LEU517; LEU520

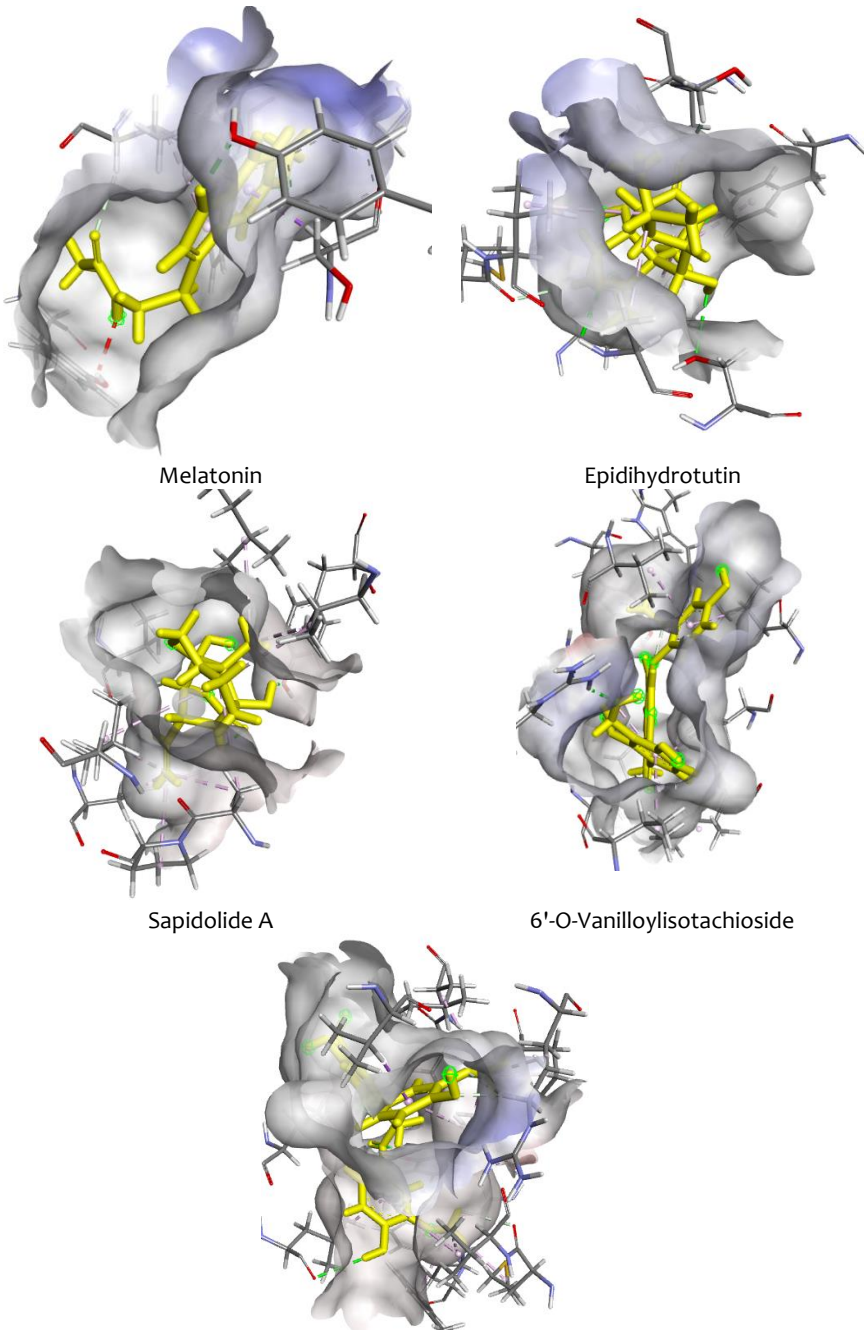

Figure 1. 3D
Structure of interaction between ligand and COX-2

In this research, several factors have been evaluated in docking studies, including hydrogen bonding, the amino acid residues involved, and bond free energies. The findings from the docking process indicated that the Astaxanthin tested had the ability to interact with the COX-2 enzyme. This linkage between the ligand and the receptor arises due to hydrogen bonds, Van der Waals attractions, and/or electrostatic interactions (Tang et al., 2018) .

The interaction between the ligand and the protein can be seen in Table 1 and Figure 2. In the native ligand, hydrogen bonding occurs between the ligand and ARG499 (2.59); LEU338 (3.31), SER339 (3.03) and hydrophobic bonds occur in VAL335(5.08); TYR341 (5.09); PHE367 (5.45); TYR371 (3.71); TRP373 (5.00); VAL509 (3.51); ALA513 (4.11). in ligand 1 the hydrogen bonds occur in TYR341 (2.20); VAL509 (2.62) and hydrophobic bonds SER339 (2.32); ALA502 (3.72); VAL509 (4.76); PHE504 (5.16). ligand 2 hydrogen bonding occurs with ALA513 (2.85); SER516 (2.77); SER339 (2.82); MET508 (2.75) and hydrophobic ALA513 (3.77); VAL509 (4.65); LEU338 (4.82); TYR334 (5.48); TYR371 (5.15). ligand 3 hydrogen interaction occurs ARG106 (3.00); TYR341 (2.99); VAL102 (2.68) and hydrophobic occur VAL335 (4.73); ALA513 (4.78); LEU517 (5.07); LEU345 (4.23); ARG106 (3.94); PRO514 (4.06); TYR341 (4.76). ligand 4 hydrogen bonds with ARG106 (2.17) and hydrophobic ILE331 (4.36); VAL335 (4.61); LEU520 (3.89); TYR371 (4.84); TRP373 (5.08); LEU338 (4.77); VAL509 (4.13); VAL102 (4.93); ALA513 (5.25). Ligand 5 TYR371 (2.42) ; LEU338 (2.63); ARG106 (2.10); SER516 (2.95); MET508 (3.00) and VAL102 hydrophobic bonds (2.72); ALA513 (3.63); ARG106 (3.82); PRO514 (3.93); LEU517 (4.40); MET508 (4.23); VAL509 (4.43); TRP373 (5.09); PHE504 (4.07); ALA513 (5.17); VAL335 (5.17); LEU338 (4.17); VAL509 (5.11).

The free energy (docking score) of the bond reflects the degree of stability of the interaction between the ligand and the cyclooxygenase enzyme in the binding site. The smaller the docking score, the higher the bond between the ligand and the receptor so that the reaction occurs easily (Fitriasari et al., 2008). Based on the best sequence in forming bonds with COX-2 is Epidihydrotutin (-50.243); Sapidolide A (-51052); Melatonin (-53039); 6'-O-Vanilloylisotachioside (-60.910) and 6'-O-Vanilloyltachioside (-61.131). so that 6'-O-Vanilloyltachioside is a potential compound as a COX-2 inhibitor.

4. Conclusion

Based on the research that has been carried out, it is known that the most potential compound as a COX-2 inhibitor from B.lanceolata is 6'-O-Vanilloyltachioside, this is because the docking score obtained is the lowest. However, this research is only a model, so further research is needed to prove the truth of this ability. The research we recommend is testing using test animals regarding the ability of 6'-O-Vanilloyltachioside as a COX-2 inhibitor so that the EC50 value can be known and can be an alternative in overcome the effects of CO-2.

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