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Evaluation of Analgesic Activity Corypalmine and Panasenoside Compounds on Cox-2 Receptors In-Silico

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ABSTRACT

Pain is a mechanism that occurs due to stimulation of nociceptors as pain receptors that cause ongoing or future tissue damage. Analgesic drugs that are usually used are COX-2 inhibitor drugs that can inhibit the activity of the COX-2 enzyme in synthesizing Prostaglandins (PG) which respond to pain and inflammation. Specific research on active compounds such as corypalmine and panasenoside related to their effects as analgesics has not been widely carried out, so it is necessary to predict the effects of both compounds by analyzing their activity on the COX-2 protein through in silico docking studies. This study aims to see the analgesic activity between the two compounds as COX-2 inhibitors. Testing was carried out through the stages of protein and ligand preparation, method validation, molecular docking of corypalmine and panasenoside compounds with COX-2 and visualization of bonds using Ligplot+. The results showed that the corypalmine docking score was more negative than panasenoside on COX-2, respectively -60.33 and -42.02. It can be concluded that the corypalmine compound is able to bind more strongly to COOX-2 and predicted to have a strong and more stable analgesic effect than panacea.

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INTRODUCTION

Pain is a mechanism that occurs due to stimulation of nociceptors as pain receptors that cause ongoing or impending tissue damage. Pain is generally characterized by an unpleasant condition and is generally a sign of impaired organ function, organ damage such as inflammation, bacterial infection, or muscle spasms (Wardoyo *et al*., 2019). Pain can come from any part of the human body, such as skin, muscles, ligaments, joints, bones, injured tissue, internal organ nerves or a combination of types of pain (The British Pain Society, 2012). Res alearch by Emril *et al*. (2018) stated that continuous pain will be felt by the world's population between developing and developed countries, with a ratio of 5.3% and 33% (WHO. 2012). WHO survey, conducted in 14 countries in each primary care center, found that the parts of the body often complained of by patients due to pain were the back, head and joints. Furthermore, two out of three patients would report pain locations in more than one part of the body. Moore RJ's study also stated that the most frequently reported locations of pain were lower back pain (40%), arthritis (24%), due to fractures (14%), and neuropathic pain (11%).

Indonesia is a country with a prevalence of individuals suffering from chronic pain, especially in the musculoskeletal area around 35.86% of the total visits of patients due to pain (Perdossi, 2007) and most of them occur in individuals who work and live in urban areas (Health Research and Development Agency, 2013). Prevention to reduce the pain consists of drugs that use algesic therapy treatment derived from both traditional and synthetic drugs (Al-Muqsith, 2015).

Synthetic drugs are artificial drugs that are made chemically, consisting of compounds that provide faster effects than herbal medicines in general. There are many aspects that must be considered in the use of synthetic drugs because their continued use can cause dangerous side effects, such as bleeding, stomach damage, hepatotoxicity, impaired kidney function, and nausea (Irawati, 2021). The use of synthetic drugs as analgesics is widely used. Analgesic drugs are usually COX-2 inhibitor drugs that can inhibit the activity of the COX-2 enzyme in synthesizing Prostaglandins (PG) that respond to pain and inflammation. Administration of selective COX-2 inhibitor drugs is thought to have an important role in pain management. Meanwhile, analgesics derived from herbal plants are known to have lower side effects when compared to synthetic analgesics. Therefore, the development of herbal-based analgesic drugs continues to be developed in order to reduce excessive side effects. This study used the active compounds corypalmine and panasenoside from the Pulai plant (Alstonia scholaris) and Panax Ginseng. Corypalmine is one of the active compounds from the Alkaloid group that has the potential as a neuroprotective, antifungal analgesic and anticholinestrase (Goel *et al.*, 2002). While panasenoside is an active compound from the flavonoid group (Flavone glycosides) which has the potential to inhibit glucose absorption that causes diabetes (Li *et al*., 2020).

Specific research related effects of corypalmine and panasenoside as an analgesic have not been widely conducted, so it is necessary to predict the effects of the two compounds by analyzing their activity on the COX-2 protein. This research aims to predict the activity of the corypalmine and panasenoside compounds in inhibiting the COX-2 protein using the in-silico molecular docking method by looking at the binding affinity of the two compounds on the COX-2 protein.

MATERIALS AND METHOD

Materials. The materials that were used in this study were COX-2 protein (protein data bank/PDB id: 4PH9) downloaded from PDB http://www.rscb.org. Then, prepare using the YASARA application. The test ligands of corypalmine and panasenoside compounds were downloaded from https://www.knapsackfamily.
com/KNApSAcK_Family/

Tools. The software used was LAPTOP-M63RGKMM (LENOVO) with specifications of an Intel(R) Celeron(R) N4020 CPU @ 1.10GHz processor, 4GB RAM, 500 Gb hard disk and Windows 11 64-bit Operating System. The software used was YASARA, PLANTS, CMD, PDB, KnAPsACK, Swiss Target Prediction, and Ligplot+.

Research Methods. In-silico is a computerized method used to predict the interaction between active compounds from a herb that acts as an analgesic. The structures of the active compounds corypalmine and panasenoside were obtained from knapsackfamily.com/. After obtaining the compound structure, target prediction of each compound was done via http://swisstargetprediction.ch/. https://www.rcsb.org/ were

used to obtain the PDB code of the protein tested. The selected protein was then validated for removing water molecules and other molecules using YASARA software. After that, molecular docking of the target protein was carried out using PLANTS software assisted by CMD (command prompt) as a container for the docking process of the PLANTS software. Validation of the docking results is categorized as good if the RMSD (Root Mean Square Deviation) value is equal to 2.5 or less than 2.5 Å (Rollando, 2018). The active ligand compound that has been prepared using Marvin Sketch and has been pronated by 10 conformations and then docked with the validated receptor results. Ligplot software was used for visualization of amino acid residues that interact with the ligand.

Data Analysis. The molecular docking result was shown by the docking score value. The docking score value revealed the strength of the interaction between the ligand and the protein. The more negative the docking score, the stronger and more stable the bond.

RESULTS AND DISCUSSION

Cyclooxygenase 2 (COX-2) with PDB code 4PH9 was the protein target protein that was obtained. Furthermore, protein preparation is carried out for separating the protein from the natural ligand, water molecules and the addition of hydrogen molecules (H). After that, preparation of the test ligand is carried out. Canonical SMILES data obtained from knapsackfamily.com/ was entered into the Marvin Sketch software to create a 2D structure of the test ligand for protonation and conformation by making 10 conformers for docking to the target protein. Preparation of the test ligand is carried out by optimizing the geometry of the structure formed which aims to obtain a stable molecular conformation, and have low potential energy that is adjusted to the conditions of the human body (Ruswanto *et al*., 2018).

Validation of the protein using YASARA software was carried out by re-anchoring the natural ligand to the original protein that has been prepared previously. The RMSD (Root Mean Standard Deviation) value <2 Armstrong was indicated as valid (Nursanti *et al*., 2022). The validation results obtained from PDB 4PH9 are 1.2886 Armstrong.

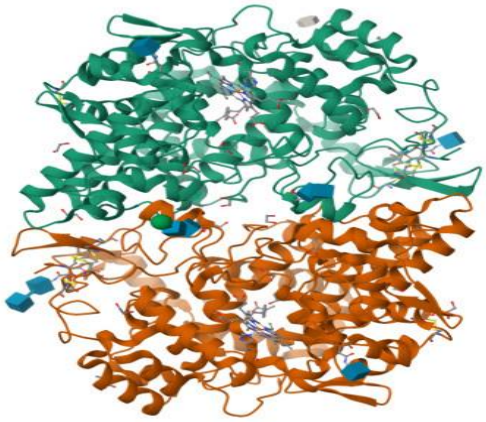

Figure 1. PDB 4PH9 form (Source RCSB)

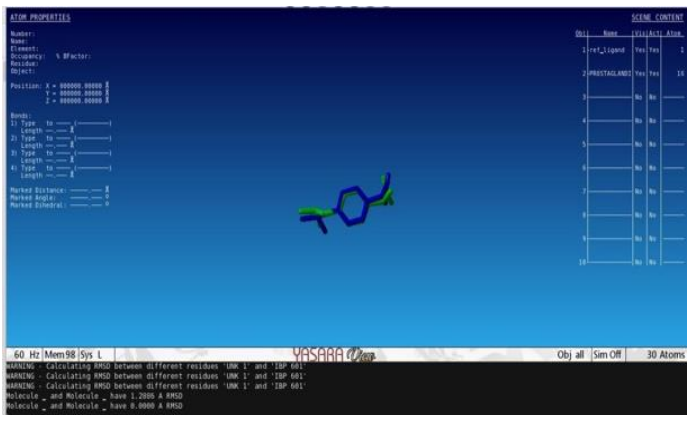

Figure 2. Validation Results of 4PH9

Based on the validation results, it shows that the 4PH9 protein was valid so that the docking process can be carried out for docking with natural ligands and test ligands (corypalmine and panasenoside). The next process was to dock the test ligands (corypalmine and panasenoside) and the natural ligands that have been prepared. The docking process was carried out using PLANTS software with CMD for the docking process. The natural ligand used was Ibuprofen (2-(4-isobutylphenyl) propionic acid) which is obtained from the separation of protein and ligand in the protein validation process. The following table shows the results of the docking scores for natural ligands and test ligands (corypalmine and panasenoside).

Table 1. Docking results of corypalmine and panasenoside compounds on the COX-2 receptor

Protein	Ligand	*Docking Score*
COX-2	Natural Ligand	-84.43
	Corypalmine	-60.33
	Panasenoside	-42.02

The docking results demonstrated that the docking scores of both corypalmine and panasenoside have different docking score values. The corypalmine docking score is more negative compared to panasenoside, which are -60.33 and 42.02 respectively. Both corypalmine and panasenoside have higher/more positive docking scores compared to natural ligands. However, corypalmine and panasenoside have fairly negative docking score values and still have affinity for the COX-2 protein because they are able to bind to COX-2 on both active sites. This docking score was used to estimate the binding energy of the complex between the ligand and the receptor. This scoring is a predictive factor for the relationship between ligand conformation, which is based on the results of the docking score taken as the best conformation/ranking determined by the lowest binding energy (most negative value). The conformation with the lowest binding energy is predicted to be the binding mode of a ligand with its receptor (Huang & Zou, 2010).

Next, Ligplot was used for 2D visualization of each ligand. This visualization aims to demonstrate the bond's interaction between each ligand and the amino acids of the target protein. The following is a visualization of the test ligand with the target protein.

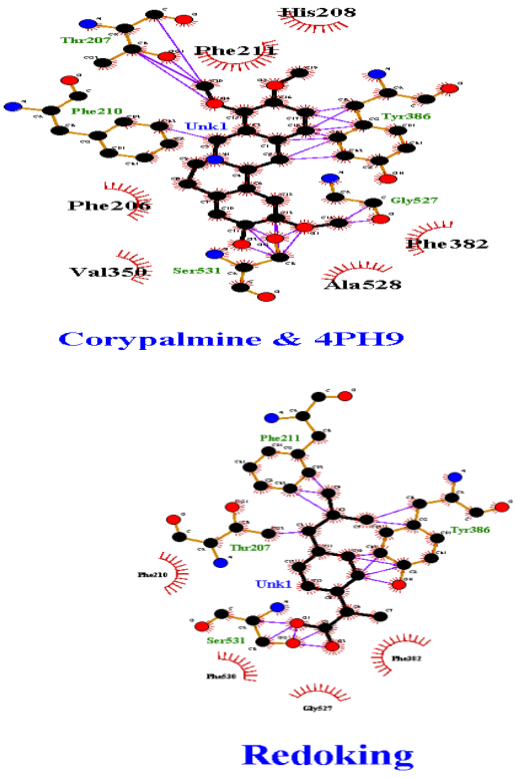

Figure 3. Visualization of Corypalmine Compound and Protein (COX-2)

Table 2. Interaction of Test Ligand (Corypalmine) and COX-2 Protein

	Ibuprofen	Corypalmine
Amino Acid	**Ser531**	**Thr207**
	Thr207	Phe210
	Phe211	**Ser531**
	Tyr386	Gly527
	-	-
	Phe210	His208
	Phe530	Phe211
	Gly527	Phe206
	Phe382	Val350
		Ala258
		Phe382

The results of 2D visualization between the Corypalmine compound and natural ligands revealed that there are hydrogen bonds with amino acids Thr207, Phe210, Ser531, Gly527 and hydrophobic bonds with amino acids His208, Phe211, Phe206, Val350, Ala258, Phe382. The interactions that occur in natural ligands (ibuprofen) are in the form of hydrogen bonds with amino acids Ser532, Thr207, Phe211 and Tyr386 and hydrophobic interactions with amino acids Phe210, Phe530, Gly527 and Phe382. While for the Corypalmine compound and natural ligands (ibuprofen) there are the same hydrogen interactions with amino acids Ser531, Thr207 and the same hydrophobic bonds with amino acids Phe382.

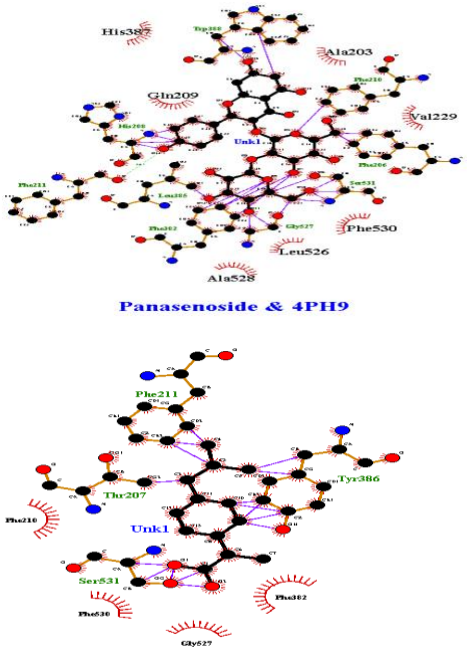

Figure 4. Visualization of penasenoside compounds and protein (COX-2)

Table 3. Interaction of Test Ligands (Penasenosides) and Proteins

	Ibuprofen	Panasenoside
Amino Acid	**Ser531**	Trp388
	Thr207	Phe210
	Phe211	His208
	Tyr386	**Phe211**
	-	Leu385
	-	Phe382
	-	Gly527
	-	Phe206
	-	**Ser531**
	-	-
	Phe210	His387
	Phe530	Gln209
	Gly527	Ala203
	Phe382	Val229
		Phe530
		Leu526
		Ala528

The results of 2D visualization that occurs between the Corypalmine compound and natural ligands show that there is a hydrogen bond with the amino acids Ser531, Phe382, Thr207 and the same hydrophobic bond with the amino acids Phe211, Phe210, Gly527. While there is the same hydrogen interaction between the panasenoside compound and natural ligand (ibuprofen) with the amino acids Ser531, Phe211, Phe530 and a hydrophobic bond with the amino acids Phe210, Gly527 and Ph382. Amino acid residues that have the same similarity to natural ligands indicated that the ligand is able to inhibit the activity of the protein target and has the same potential as the native ligand as an inhibitor (Lipinski et al., 2001). Therefore, based on the results of the study, the active compounds corypalmine and panasenoside have the potential as analgesics by inhibiting the COX-2 protein.

CONCLUSION

Based on the results of this study, it can be concluded that the active compound corypalmine is estimated to have better potential as an analgesic compared to the active compound panasenoside against COX-2 with docking scores of -60.33 and 42.02, respectively.

AUTHORS CONTRIBUTION

Lesbata designed and conducted the research, analyzed and interpreted the data, and wrote the draft of the manuscript. Watuguly, Kakisina, and Anggraeni designed the research, analyzed and interpreted the data, reviewed the draft of the manuscript, and supervised all the process.

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