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ORIGINAL ARTICLE

ANTI-INFLAMMATORY PREDICTION OF PERONEMIN COMPOUNDS FROM SUNGKAI (*Peronema canescens* Jack) AND THEIR DERIVATIVES

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Abstract Seven Sungkai Peronemins compounds belong to the alkaloid group, Peronemin A2, A3, B1, B2, B3, C1, and D1. Sungkai contains several bioactive compounds, triterpenoids, alkaloids, flavonoids, phenolics, steroids, and saponins which can act as anti-inflammatory candidates. Geometry optimization to find the most stable molecular structure and SMILES of the peronemin compound was used to predict pIC50 using the pChEMBL® program. From the test results of seven peronemin compounds, several candidate target molecules were obtained as potential anti-inflammatory agents, namely Angiotensin II type 2 (AT-2) receptors, Dihydrofolate reductase, and Phosphodiesterase 7A. Of the three target molecules, the Angiotensin II type 2 (AT-2) receptor on peronemin C1 has the highest pIC50 value of 6.79. The highest pIC50 value indicates an exponentially potent inhibitor in determining its biological activity. The anti-inflammatory function of AT-2 is revealed by its involvement in modulating mediators such as cytokines and chemokines.

Keywords: Anti-Inflamasi, Peronemin, Sungkai, pChEMBL, Angiotensin II type 2 (AT-2)

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Introduction

Indonesia is a country that has abundant natural resources, and around 40.000 plant species have potential as medicine. Most of the living natural resources in Indonesia, only around 2.5%, have been explored and used as medicine or alternative healing (Pindan et al., 2021). One of the plants that can use as an alternative treatment is Sungkai. Sungkai is a plant endemic to Kalimantan which can also be found in West Sumatra, Bengkulu, Jambi, South Sumatera, and West Java (Wirman et al., 2022). Young sungkai leaves are usually used as a mouthwash, fever, and worms (ringworms). Sungkai contains secondary metabolite compounds involved in homeostatic processes; these processes are closely related to the immune system (Subandrate et al., 2022). Halim et al. (2020) state that Sungkai leaves contains kleros-type furano diterpenoid compounds and (clerodane). Sungkai has seven new Peronemin compounds and their derivatives which belong to the alkaloid group, namely Peronemin A2, A3, B1, B2, B3, C1, and D1. Peronemin can boost the immune system by increasing the number of white blood cells (leukocytes) in the body. Leukocyte cells

form blood components, which help increase levels of white blood cells that can protect the body from various diseases (Bahri et al., 2021). In addition, Sungkai leaves contain bioactive compounds like triterpenoids, alkaloids, flavonoids, phenolics, steroids, and saponins (Yeni et al., 2022). These bioactive compounds act as anti-inflammatory candidates. Inflammation is a natural immune reaction in the body to fight disease and harmful microorganisms. This inflammation occurs with the migration of leukocyte cells from the blood circulation in the area of inflammation (Latief et al., 2021).

Healing inflammation is done by relieving pain or stopping tissue damage by taking drugs. The content of flavonoids, saponins, alkaloids, and phenols in Sungkai leaves is thought to have anti-inflammatory activity. Inflammation occurs, characterized by the migration of leukocyte cells from the blood circulation in the area of inflammation. Anti-inflammatory activity can be analyzed in vivo by observing decreased leukocyte cells in the inflammatory site (Latief et al., 2021). According to research by Ma et al. (2020), regarding identifying target molecules (receptors) in cannabidiol compounds that will be tested to determine their anti-inflammatory activity, prediction can be made using the Swiss Target Prediction webserver. Swiss Target Prediction predicts bioactive small molecule targets in living things. The Swiss Target Prediction web server helps understand the molecular mechanisms underlying a particular phenotype or bioactivity to rationalize possible side effects or to predict known molecular targets. A compound's potency test can also be carried out using the W2Drug Pass online web server. This web-based application evaluates a compound's biological potential (Istiqomah and Fatikasari, 2023). In this study, prediction of the anti-inflammatory properties of peronemin in rivers was carried out using the pChEMBL® program. The pChEMBL® program is a web server designed to predict the pIC50 value of small molecules on several protein targets based on the QSAR.

Materials and Methods

Compound Structure

Seven Peronemin compounds used as the main ingredient in this study were made into two-dimensional (2D) structures using the ChemDraw Ultra 12.0 program. The seven peronemine compounds will produce potential biological activity seen from the structural energy of the compounds at optimal conditions with a low value, making it easier to calculate the algorithm. Potential biological activity predicted using the pChEMBL® webserver. The SMILES code obtained from the 2D structure of seven peronemin compounds using ChemDraw Ultra 12.0 software is entered into the pChEMBL® program to predict pIC50 values . It will generate several candidate target molecules that have the potential as anti-inflammatory agents.

Predictor Calculations

Calculations are obtained from the pChEMBL® program by entering the SMILES code. The analysis used is a multilinear regression with a net atomic charge (q) as the independent variable for the active anti-inflammatory compound from peronemin derivatives, which can be expressed as a log value (1/IC50) that functions as the dependent variable. Single-point calculations were performed using the pChEMBL® program on an optimized structure to obtain the electronic parameter (σ) in the form of the net atomic charge (q) contained in the molecule. From the regression analysis, an equation obtained that can explain the relationship between the structure and activity of peronemin-derived compounds, as well as choosing a good regression test value (R2), with a range of R2 values ≥ 0.8 with a pIC50 value ranging from 0.6-0.9 for enzymes /precursors involved in the anti-inflammatory bioactivity test of the seven Peronemin compounds tested (Ahmad and Alam, 2011).

Results and Discussion

The Sungkai plant (*Peronema canescens* Jack) is an ethnobotanical plant often used as a source of traditional medicine for the people of Indonesia. Sungkai plants can be found in Kalimantan and Sumatra (Latief et al., 2021). Sungkai leaf extract in acetone produces secondary metabolites in the form of peronemin. Peronemin is a secondary metabolite of the alkaloid group and has efficacy as an antimalaria, anti-fever, and antibacterial drug. Sungkai leaf extract produces active compounds in the form of β-sitosterol, phytol, β-amyrin and peronemins A2, A3, B1, B2, B3, C1, and D1 (Ibrahim et al., 2021). Figure 1 shows the 2D structure of the seven peronemin compounds that will be tested for their biological activity potential using the pChEMBL® webserver. Data on the prediction results of peronemin compounds are in Table 1.

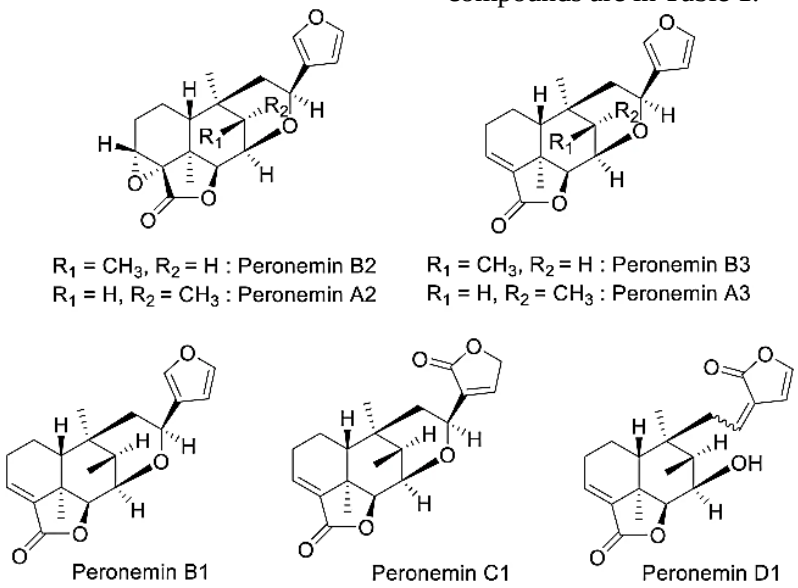

Figure 1. Peronemin structure and derivates

Table 1. Prediction of the potential bioactivity of peronemin compounds and their derivatives

Protein target	pIC_{50}	∑ Dataset	R^2 test	Drug/Clinical Candidates	Bioactivities
Peronemin A2 and B2					
Tissue factor pathway inhibitor	8.07	3382	0.83	ND	Anticoagulant (*Blood Clotting*)
Voltage-gated potassium channel subunit Kv1.3	7.02	801	0.85	ND	Cancer therapy
Angiotensin II type 2 (AT-2) receptor	6.73	690	0.83	ND	Anti-Inflammatory and Lowers blood pressure (Hypertension)
Calcitonin gene-related peptide type 1 receptor	6.56	744	0.83	Olcegepant (10.70), Telcagepant (8.70)	Migraine medication Monoclonal antibodies
Protein kinase C beta	6.35	647	0.8	Enzastaurin (8.22), Ruboxistaurin (8.33)	Anticancer
Apoptosis regulator Bcl-2	6.21	888	0.87	Venetoclax (8.13), Navitoclax (8.70)	Anti-apoptotic Anticancer
Peroxisome proliferator-activated receptor delta	6.03	638	0.88	Gw501516 (9.00)	Therapeutic preventive agent, treating metabolic diseases, inflammation, and cancer

Serine/threonine-protein kinase/endoribonuclease IRE1	6.03	670	0.87	ND	Antibodies, immunogens
Dihydrofolate reductase	5.94	1027	0.93	Methotrexate (MTX)	Anticancer, as an anti-inflammatory and immunosuppressive agent, anti-folate, anti-malarial
Serine/threonine-protein kinase RAF	5.92	1248	0.83	Regorafenib (8.82)	Anticancer
Peronemin A3, B1, and **B3**					
Calcitonin gene-related peptide type 1 receptor	9.65	744	0.83	Olcegepant (10.70), Telcagepant (8.70)	Migraine medication Monoclonal antibodies
Tissue factor pathway inhibitor	8.28	3382	0.83	ND	Anticoagulant (*Blood Clotting*)
Voltage-gated potassium channel subunit Kv1.3	6.63	801	0.85	ND	Cancer therapy
Phosphodiesterase 5A	6.51	1987	0.83	Vardenafil Hydrochloride (9.15), Sildenafil Citrate (8.66), Gisadenafil (8.91), Avanafil Tadalafil (8.92)	Cardiovascular disease, impotence/erectile dysfunction
Apoptosis regulator Bcl-2	6.42	888	0.87	Venetoclax Navitoclax	Anti-apoptotic Anticancer
Phosphodiesterase 7A	6.34	621	0.8		Anti-Inflammatory
Dihydrofolate reductase	6.3	1442	0.83	Methotrexate (MTX)	Anticancer, as an anti-inflammatory and immunosuppressive agent, anti-folate, anti-malarial
Angiotensin II type 2 (AT-2) receptor	6.25	690	0.83		Anti-Inflammatory
Peroxisome proliferator-activated receptor delta	6.23	638	0.88	Gw501516	PPAR-delta is a nuclear hormone receptor that regulates various biological processes involved in the development of several chronic diseases
Serine/threonine-protein kinase WEE1	6.21	578	0.91	Adavosertib	Anticancer
Peronemin C1					
Calcitonin gene-related peptide type 1 receptor	9.43	744	0.83	Olcegepant(10.70) , Telcagepant(8.70)	Monoclonal antibodies Anti-CGRP (Migraine)
Apoptosis regulator Bcl-2	7.39	888	0.87	Venetoclax(8.13) ,Navitoclax(8.70)	Anticancer
Angiotensin II type 2 (AT-2) receptor	6.79	690	0.83	ND	Anti-Inflammatory and Lowers blood pressure (Hypertension)
Serine/threonine-protein kinase RAF	6.31	1248	0.83	Regorafenib (8.82)	Anticancer

Phosphodiesterase 7A	6.31	621	0.8		Anti-Inflammatory
Dihydrofolate reductase	6.25	1442	0.83		Antibiotics
Peroxisome proliferator-activated receptor delta	6.03	638	0.88	GW501516(9.00) (obat peningkat kinerja ergogenic)	PPAR-delta is a nuclear hormone receptor that regulates various biological processes involved in the development of several chronic diseases
Protein kinase C beta	5.95	647	0.8	Enzastaurin(8.22), Ruboxistaurin (8.33)	Anticancer
Serine/threonine-protein kinase WEE1	5.81	578	0.91	Adavosertib(8.28)	Anticancer
Endothelin receptor ET-B	5.81	1039	0.9	Darusentan(7.80), Tezosentan(7.68)	Overcoming high blood pressure (hypertension) Heart failure, and angina.
Peronemin D1					
Calcitonin gene-related peptide type 1 receptor	7.66	744	0.83	Olcegepant(10.70) , Telcagepant(8.70)	Monoclonal antibodies Anti-CGRP (Migraine)
Phosphodiesterase 7A	6.34	621	0.8		Anti-Inflammatory
Apoptosis regulator Bcl-2	6.22	888	0.87	Venetoclax(8.13), Navitoclax(8.70)	Anticancer
Serine/threonine-protein kinase WEE1	6.07	578	0.91	Adavosertib(8.28)	Anticancer
Estradiol 17-beta-dehydrogenase 2	6.06	627	0.84	ND	Anti-Osteoporosis
Angiotensin II type 2 (AT-2) receptor	6.04	690	0.83	ND	Anti-Inflammatory and Lowers blood pressure (Hypertension)
Serine/threonine-protein kinase RAF	6.03	1248	0.83	Regorafenib (8.82)	Anticancer
Voltage-gated potassium channel subunit Kv1.3	5.94	801	0.85	ND	Cancer therapy
Peroxisome proliferator-activated receptor delta	5.71	638	0.88	GW501516(9.00) (Obat Peningkat Kinerja Ergogenic)	PPAR-delta is a nuclear hormone receptor that regulates various biological processes involved in the development of several chronic diseases
Dihydrofolate reductase	5.69	1442	0.83	ND	Anti-cancer, anti-inflammatory

Inflammation is a normal protective response to tissue injury caused by physical trauma, damaging chemicals, or microbiological activity (Dewi et al., 2015). Inflammation is, therefore, a defense mechanism that is vital to health. Inflammation can be treated using steroid-class anti-inflammatory drugs (AIS) and non-steroidal anti-inflammatory drugs (NSAIDs). Utilization of medicinal plants that have potential as anti-inflammatories used as alternative treatments that are relatively smaller in side effects (Pramitaningastuti et al., 2017). The prediction of Seven peronemin compounds in Sungkai plants can be analyzed using the pChEMBL® program to produce a dataset in the form of target molecules, pIC50 values, and

bioactive activities of the peronemin compounds tested.

The data obtained from the prediction results using the pChEMBL® program were processed to determine peronemin anti-inflammatory activities. This prediction was made by looking at the pIC50 value of each of the tested peronemin compounds. The IC_{50} value has a concentration where the ligand (drug or extract) that can inhibit the enzyme is 50%. Meanwhile, the pIC_{50} value is a new approach used to check logarithmically the same data. A higher pIC_{50} value indicates an exponentially strong inhibitor. The pIC_{50} value in this prediction is considered to have good precision when compared to IC_{50} in determining biological activity (Munaya et al., 2022). When the IC_{50} value is correlated with drug potency, it is the amount of drug needed to produce a good result with a small effect. The lower the IC_{50} value, the better the activity. Whereas at pIC_{50} a higher value indicates the best activity.

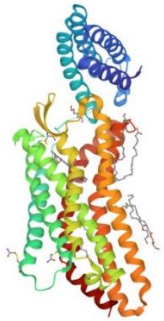

Figure 2. 3D Structure of Angiotensin II type 2 (AT-2) receptor

From the test results for peronemin compounds A2, A3, B1, B2, B3, C1, and D1, several candidate target molecules with potential anti-inflammatory agents were obtained. Some of these target molecules are the Angiotensin II type 2 (AT-2) receptor, Dihydrofolate reductase, and Phosphodiesterase 7 A. Angiotensin II type 2 (AT-2) is the receptor with the highest pIC50 value of the three target molecules. The 3D structure of the angiotensin II type 2 (AT-2) receptor is shown in Figure 2. The angiotensin II type 2 (AT-2) receptor in the peronemin C1 compound has the highest pIC50 value of 6.79; when the pIC50 value is high, it indicates a weak inhibitor. to determine its biological activity.

According to Rompe et al. (2015), the angiotensin II receptor type 2 (ATR2) is an endogenous repair system because it can regulate tissue damage and protect tissue. Angiotensin II type 2 (ATR2) receptors can act as anti-proliferative, anti-inflammatory, anti-fibrotic, and anti-apoptotic. Previous studies have shown that the AT2R receptor can regulate tissue inflammation in synovial rheumatoid arthritis (RA). This study explains that the imbalance between pro-inflammatory and anti-inflammatory cytokines that will support pro-inflammatory cytokines (IL-1β and TNF-α) is involved in the pathogenesis of RA. The balance between pro and anti-inflammatory cytokines is the target of healing in RA. Angiotensin II type 2 (ATR2) will activate Angiotensin II type 1 (ATR1), which will result in the production of reactive oxygen species and activation of NF-kB, which leads to the production of inflammatory cytokines (Mostafa et al., 2020).

Patel et al. (2021) also stated that the anti-inflammatory function of Angiotensin II type 2 had been proven by its involvement in modulating mediators such as cytokines and chemokines which can form communicative pathways between non-immune cells and innate and immune cells adaptive. This study states that anti-inflammatory mediated by Angiotensin II type 2 has promising activity in myocardial infarction and heart repair.

Conclusion

The tests that were carried out using the pChEMBL® program showed that the compound peronemin C1 had a high potential as an anti-inflammatory. This was found in the tests where the peronemin C1 compound has a high pIC50 value on its target molecule in the form of Angiotensin II type 2. Angiotensin II type 2 can function as an anti-inflammatory by activating Angiotensin II type 1 (ATR1), which will

produce reactive oxygen species and activation of NF kB, leading to inflammatory cytokine production.

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

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