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Systemic Anti-inflammatory Activity of American Cockroach (*Periplaneta americana*) Extract: A Molecular Docking Study

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ABSTRACT

Surgery can trigger systemic inflammatory response syndrome. This study aims to determine the effectiveness of *Periplaneta americana* cockroach extract as an oral systemic anti-inflammatory agent using molecular docking. The molecular docking method consisted of five steps. The first step was preparing the TNF-α converting enzyme (TACE) receptor as a native ligand, dexamethasone as a control ligand, and three test ligands of *Periplaneta americana* cockroach extract. The second step was docking preparation. The third step was analyzing Gibbs free energy (ΔG) and root mean square deviation (RMSD). The fourth step was docking the test and control ligands with TACE. The fifth step was analyzing ΔG, inhibition constant (Ki), visualization of two- and three-dimensional interactions, percentage of binding site similarity (%BSS), and the rule of five (Ro5) on test ligands. The ΔG results for the native, control, and test ligands 1, 2, and 3 were -12.8, -7.1, -7.7, -6.9, and -9.0 kcal/mol, respectively. The Ki values for the native, control, and test ligands 1, 2, and 3 were 4.091, 6.205, 2.253, 9.521, and 2.507 μM, respectively. The results of the Ro5 analysis suggested that the three test ligands satisfied Lipinski's rule of five. This study concluded that *Periplaneta americana* cockroach extract is an effective oral systemic anti-inflammatory agent.

Keyword: American cockroach *Periplaneta americana*, molecular docking, systemic inflammatory response syndrome, TNF-α converting enzym

INTRODUCTION

Effective therapy management after surgery is critical due to the potential for complications, including systemic inflammatory response syndrome (SIRS). SIRS is a physiological, pathological, and biochemical abnormality that results from a hyperinflammatory response to infection or non-infection (Kosyreva et al., 2020). The pathogenesis of SIRS after surgery begins with an acute phase reaction due to endothelial damage, which can lead to endothelial dysfunction, bleeding, and cell damage in the surgical area. Endothelial dysfunction is associated with

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proinflammatory cytokines which trigger inflammation (Andriyono, 2019). If SIRS occurs and is not appropriately treated, it can lead to multi organ dysfunction syndrome (MODS) (Margraf *et al.,* 2020; Zhang *et al.,* 2016).

Tumor necrosis factor-alpha (TNF-α) is a pleiotropic cytokine that contributes to cellular immunity and inflammatory responses (Ramana, 2010). TNF-α activation is triggered by the activity of the TNF-α converting enzyme (TACE), which is part of A Disintegrin and Metalloproteinase (ADAM), a protein involved in the degradation of protein membranes during inflammatory processes (Chemaly et al., 2017). TACE is involved in TNF-α receptors 1 and 2. ADAM expression is increased in patients with sepsis, while TACE expression is increased in patients with ischemia, heart damage, arthritis, and impaired immunity (Delanghe & Speeckaert, 2022).

Research on the use of *P. americana* cockroaches as a raw material for medicinal drugs in Indonesia has never been conducted. Therefore, it is necessary to conduct this study. Previous studies have shown that *P. americana* cockroach extract has potential as an antitumor, immunity-booster, analgesic, tissue repair, and SIRS treatment (Zhang et al., 2016; Xue et al., 2020). This study used molecular docking to analyze the potential efficacy of *P. americana* cockroach extract as a treatment for systemic inflammation associated with postoperative SIRS. The test ligands analyzed in this study are three compounds with biological activity, namely 2-isopropoxy-5-phenyl-1,3,4-oxadiazole; 2-amino-3,6-dimethylimidazo[4,5-b]pyridine; and 4,4'-(iminomethylene)bis(N,N-dimethylaniline) or Auramine O (Ali *et al.,* 2017). The results of this study can serve as a basis for further research in animal models.

MATERIALS AND METHODS

This study used the TNF-α converting enzyme (TACE) receptor obtained under PDB ID of 3EWJ by means of X-ray crystallization. The receptor has a native ligand, (1S,3R,6S)-4-oxo-6-{4-[(2-phenylquinolin-4-yl)methoxy]phenyl}-5-azaspiro[2.4]heptane-1-carboxylic acid or carboxylate. The crystallization method used was X-ray diffraction with a resolution of 1.8 Armstrong (Guo et al., 2009). The control ligand used was dexamethasone. The test ligands used were 2-isopropoxy-5-phenyl-1,3,4-oxadiazole ($C_{11}H_{12}N_2O_2$) (test ligand 1), 2-Amino-3,6-dimethylimidazo[4,5-b]pyridine ($C_8H_{10}N_4$) (test ligand 2), and 4,4'-(iminomethylene)bis(N,N-dimethylaniline) or Auramine O ($C_{17}H_{22}ClN_3$) (test ligand 3). The three-dimensional protein structures of the receptor and ligands were downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and RCSB PDB (https://www.rcsb.org/). Docking was performed using the Vina method with Discovery Studio software (v17.2.0.16349), Autodocktools (v.1.5.6), and AutodockVina (v.1.5.6).

This study used the molecular docking method. The first step involved identifying native, control, and test ligands. The receptor and ligands were obtained from previous studies. The second step involved preparing the docking by removing water molecules and adding hydrogen molecules. The third step, which is validation, involved analyzing Gibbs free energy (ΔG) values and root-

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mean-square deviation (RMSD). The fourth step involved docking the test and control ligands ten times. Finally, the fifth step involved evaluating the quality of the model.

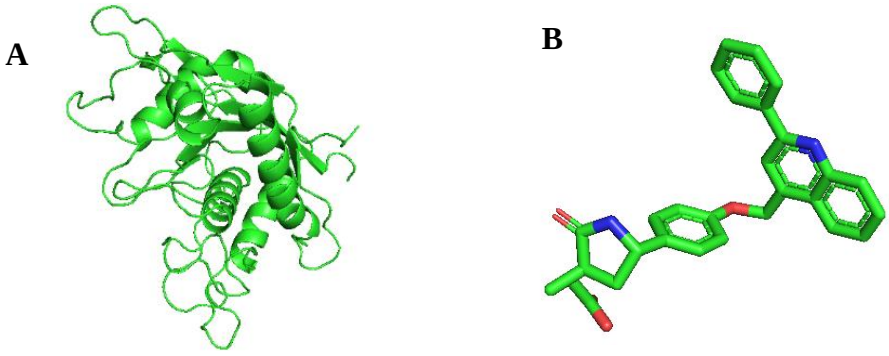

Figure 1. Three-dimensional visualization of TACE receptor (A) and native ligand (B)

The analysis and evaluation of the test ligands included the calculation of ΔG values and inhibition constant (Ki), visualization of interaction between ligands and receptor, analysis of percentage of binding site similarity (%BSS) and Lipinski's rule of five (Ro5) (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp). Ki values was calculated using the following equation: ΔG = RTInKi, where ΔG (kcal/mol), R (general gas constant) = 1.986 cal/MolK, and T (temperature, kelvin) = 298.15 K (Kalontong **et al.,** 2022). The %BSS was calculated by dividing the number of amino acid residues of the native ligands by the number of amino acid residues of the control ligands and multiplying it by 100%.

RESULTS AND DISCUSSION

The resolution of the TACE receptor was less than 2.5 Amstrong, indicating a similarity to existing structures in the cells (Umamaheswari et al., 2013). In this study, the native ligand was removed so that the receptor was not bound to the native ligand.

The ΔG values for the docking of the TACE receptor with native, control, and test ligands are presented in Table 1. The ΔG analyzed for carboxylate used the first conformation value, while the ΔG of control ligands and test ligands used the second conformation value (Trott & Olson, 2010). ΔG values indicate the strength of the bond between the ligand and the receptor. The more negative the ΔG value, the stronger the bond formed between the ligand and the receptor (Aziz, 2020). According to the results of ΔG values, carboxylate as a native ligand was found to have the most negative ΔG, indicating that the bond between carboxylate and the TACE receptor was the stronger compared to dexamethasone and three test ligands. Moreover, the comparison between the test and control ligands found that the bonds between test ligands 2 and 3 and the TACE receptor were stronger compared to dexamethasone.

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Table 1. Variables of interaction between ligands and TACE receptors

Variable	Native ligand	Control ligand	Test ligands		
			1	2	3
ΔG (kcal/mol)	-12.8	-7.1	-7.7	-6.9	-9.0
Ki (μM)	4.844	6.205	2.451	8.701	2.773
Hydrogen bond of amino acid residues	TYR 436	ALA439 PRO437 ILE438	-	PRO437	TYR433
Bond distance (Å)	3.26532	2.33712 2.82928 3.18029	-	3.75413	2.69547
Hydrophobic bond of amino acid residues	LYS432 HIS444, LYS432, LYS432, ILE438, VAL440	ILE438*, ALA439, ALA439, ALA439, LEU348, LEU348	ALA439, HIS405, HIS405, ALA439, VAL402, HIS405, HIS415, LEU401, VAL434, ALA439	ALA439, HIS405, HIS405, LEU401, VAL434, VAL402, ALA439	LYS432*, LEU401, ALA439
%BSS	100%	9%	0%	0%	9%

Note: Native ligand ((1S,3R,6S)-4-oxo-6-{4-[(2-phenylquinolin-4-yl)methoxy]phenyl}-5-azaspiro [2.4] heptane-1-carboxylic acid or carboxylate), control ligand (dexamethasone), test ligand 1 (2-isopropoxy-5-phenyl-1,3,4-oxadiazole), test ligand 2 (2-amino-3,6-dimethylimidazo[4,5-b]pyridine), and test ligand 3 (4,4'-(iminomethylene)bis(N,N-dimethylaniline or Auramine O)

Furthermore, according on the results of Ki values, test ligand 3 was found to have the smallest value. Test ligands 1 and 3 had smaller Ki values compared to carboxylate and dexamethasone, indicating their superior ability to inhibit the TACE receptor. The calculation of Ki aims to predict the inhibitory potential of a compound on its receptors, with a smaller Ki value indicating a stronger ability to inhibit receptors (Umamaheswari et al., 2013).

The percentage of binding site similarity (%BSS) was used to analyze the ability of the TACE receptor to interact with the ligands. Amino acid residues with similar active sites can potentially affect the function of the receptor upon ligand binding (Ferdian et al., 2021). The results of this study found that the similar active sites between the native, control, test ligands were ILE438 (control ligand) and LYS432 (test ligand 3) (Table 1). The %BSS value of test ligand 3 was similar to that of the control ligand.

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Figures 2 and 3 shows the visualization of the receptor and ligands. The ligands are represented by the blue area, while the active site of the TACE receptor interacting with the ligands is represented by the orange area. The bonds were analyzed for their ability to interact. Despite the distance between the receptor and ligands, hydrogen bonding could occur because it is strong enough to facilitate interaction between the ligands and receptor. A hydrophobic bond is a reflection of the stability of the bond between the ligands and receptor. Based on the analysis of bond interaction, this study found that the control ligand had more hydrogen bonds than the test ligands.

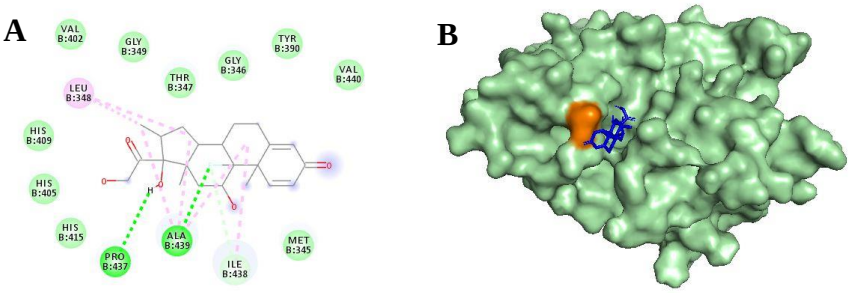

Figure 2. Visualization of interaction between TACE and two-dimensional (A) and three-dimensional (B) control ligands

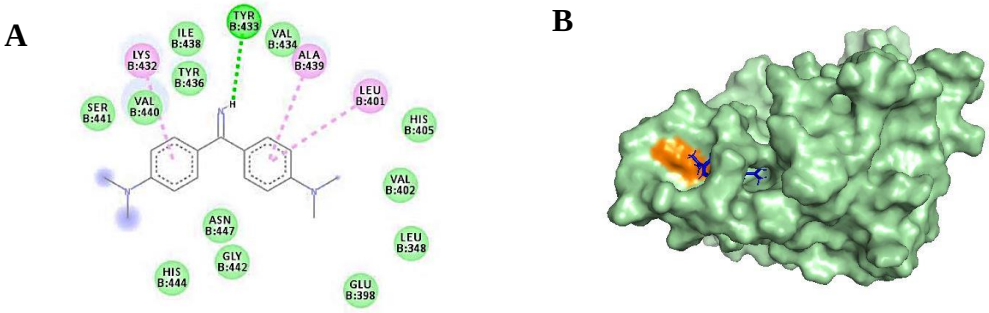

Figure 3. Visualization of interaction between TACE two-dimensional (A) and three-dimensional (B) test ligands

The results of the analysis of Lipinski's rule of five (Ro5) were used to predict the bioavailability of ligand molecules tested with orally administered drug compounds. A drug candidate is considered suitable for oral administration if it meets at least four of five criteria, namely molar mass of less than 500 Daltons, high lipophilicity (LogP < 5), hydrogen bond donor of less than 5, hydrogen bond acceptor of less than 10, and molar refractivity between 40 and 130 (Lipinski, 2004; Jayaram et al., 2012). The

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results of Ro5 analysis on the test ligands found that they met all Ro5 criteria, suggesting that the ligands in *P. americana* cockroach extract had good bioavailability and was suitable for oral administration (Table 2).

Table 2. Analysis of Lipinski's rule of five in three test ligands

Criteria of Ro5	Test ligand 1	Test ligand 2	Test ligand 3
Molar mass (Dalton)	204	162	267
Lipophilicity (LogP)	2.5238	0.858920	3.234769
Hydrogen donor bonding	0	2	1
Acceptor hydrogen bonding	4	3	3
Molar refractivity	55.497990	47.658398	87.468674

Note: Test ligand 1 (2-isopropoxy-5-phenyl-1,3,4-oxadiazole), test ligand 2 (2-amino-3,6-dimethylimidazo[4,5-b]pyridine), test ligand 3 (4,4'-(iminomethylene)bis(N,N-dimethylaniline or Auramine O)

Dexamethasone was used as a control ligand in this study. It is a corticosteroid drug commonly administered orally or injected to humans and animals. Its extensive drug activity includes glucocorticoid replacement therapy for patients with adrenal gland insufficiency, anti-inflammation, and immunosuppressant. Dexamethasone is commonly used as an anti-inflammatory agent in acute inflammatory responses (Baniadam et al., 2021; Kaka et al., 2018).

CONCLUSION

This study concluded that *Peiplaneta americana* cockroach extract was effective as an oral systemic anti-inflammatory agent after surgery, according to the results of the molecular docking that analyzed Gibbs free energy, inhibition constant, and Lipinski's rule of five.

APPROVAL OF ETHICAL COMMISSION

This study did not require an ethical clearance as it did not involve experimental animals and was conducted using only computational methods.

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