Antipyretic Drug Candidates Through Reverse Docking Techniques Used In Science Learning

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Abstract: Red ginger (Zingiber officinale var. Rubrum) is a commonly used rhizome known for its fragrant and spicy taste. It contains gingerol and shogaol compounds that have antipyretic effects by inhibiting prostaglandin formation and stimulating the production of interleukin-10, an endogenous antipyretic. This study aimed to evaluate the potential of gingerol and shogaol compounds as antipyretic drug candidates through reverse docking techniques targeting interleukin-10 (IL-10). Ten natural compounds from red ginger were predicted for their potential as antipyretic drugs and docked with the IL-10 receptor protein using various computer programs. The molecular docking results showed that (6)-shogaol had four amino acid bond residues that were the same as the ibuprofen control compound, indicating its potential as an antipyretic drug candidate. Furthermore, (6)-shogaol had the same binding affinity as the control compound and was safe for oral consumption based on pharmacokinetic and toxicity tests using Lipinski’s Rule, Toxtree, and admet-T. These findings suggest that (6)-shogaol is a promising antipyretic drug candidate compared to other compounds. In conclusion, this study identified the potential of (6)-shogaol as an antipyretic drug candidate through reverse docking techniques targeting interleukin-10. Red ginger could provide a natural alternative for antipyretic drugs, and further research is recommended to explore the role of gingerol and shogaol compounds in targeting other proteins.

Keywords: Antipyretic; Gingerol; Red ginger; Reverse docking technique Shogaol

Introduction

Red ginger (Zingiber officinale var. officinale), Rubrum) is one of the varieties that is cultivated and widely circulated in Indonesian society (Suharti et al., 2022). The red ginger plant that is often used by the community is the rhizome part because it has many uses including as a cooking spice, farms industry, perfume and cosmetics (Ivanović et al., 2021). Red ginger contains gingerol and shogaol which makes the distinctive taste fragrant and spicy taste (Gao et al., 2022). The characteristic of gingerol is that it is unstable at high temperatures and will be hydrated into shogaol (Syafitri et al., 2018). The content of gingerol and shogaol compounds in red ginger can provide an antipyretic effect by inhibiting the formation of prostaglandins and stimulating the production of interleukin-10 which is an endogenous antipyretic.

Interleukin-10 (IL-10) is a cytokine that is widely secreted by monocytes by having a pleiotropic effect on the immune system and inflammation. The first time IL-10 was known for its ability to inhibit the activation and effector function of T cells, monocytes and macrophages (Saxton et al., 2021). In addition, IL-10 also inhibits or reduces the inflammatory response, controls the development and differentiation of B cells, NK cells, TH cells, CD 8 T cells, mastocytes, granulocytes, dendritic cells, keratinocytes, and endothelial cells, and is immunosuppressive to myeloid cells (Lobo-Silva et al., 2016). Inhibition of prostaglandins by inhibiting the activity of cyclooxygenase and lipoxygenase in arachidonic acid, causing a decrease in the number of prostaglandins and leukotrienes. The inhibitory activity of ginger extract against prostaglandin synthesis turned out to be analogous to the activity of synthetic antipyretic drugs.

How to Cite:
In herbal therapy, ginger rhizomes have a warming effect as the basis of diaphoretic activity, which can stimulate increased heat expenditure from the body so that it can eventually lower body temperature in a feverish state. Ginger and its components also have the effect of stimulating thermoregulatory receptors (Novoselova et al., 2018).

Fever can be overcome by treatment used to restore the temperature of the body's normal temperature which is 37°C. Antipyretic drugs are mostly used to help restore to normal body temperature by inhibiting the synthesis and release of prostaglandin E2 and increasing the production of interleukin 10 yang can mediate the effects of endogenous pyrogens in the hypothalamus (Prajitha et al., 2019). Antipyretics can generally be classified as the salicylic group (aspirin, salicylamide), the para-aminophenol group (e.g., acetaminophen, phenacetine) and the pyrazalol group (e.g., A phenylbutazone and methazol). The most widely used antipyretic drugs are ibuprofen (Dinç et al., 2020a).

The use of synthetic drugs can cause various health problems if it exceeds the prescribed dosage. Side effects of ibuprofen use are gastric disorders, diarrhea, vomiting, dizziness, skin rashes, blood loss, sometimes peptic ulcers, and urinary retention. Ibuprofen has also been reported to result in renal dysfunction, especially in patients with a history of kidney disease, heart failure and liver sorosis (Dinç et al., 2020b). The World Health Organization (WHO) recommends using traditional or herbal medicine to maintain public health. The use of traditional medicine is considered safer than synthetic drugs because it has relatively fewer side effects if used appropriately (Dinç et al., 2020b). One of the plants developed as a folk remedy for reducing fever is the rhizome of the red ginger plant (Zingiber officinale Rosc. Var. Rubrum).

To determine the potential of the gingerol and shogaol compounds as antipyretics, molecular docking is necessary. Molecular docking is a computation used to predict whether a compound has appropriate activity before it is tested. This experiment using molecular docking aims to assess the potential of the natural compounds gingerol and shogaol as candidate antipyretic drugs.

**Method**

This research utilized the reverse docking technique to analyze the potential compounds gingerol and shogaol in red ginger (Zingiber officinale Rosc. Var. Rubrum) against interleukin-10 (IL-10) as an antipyretic drug candidate (Dinç et al., 2020b). The research employed a qualitative descriptive approach, utilizing relevant literature studies and specialized software (Hong et al., 2018; Vindrola-Padros & Johnson, 2020). The computer used had Intel® Core i3 CPU specifications, 2.30 GHz, 4GB memory, and operated on the Windows 8 operating system. The software utilized included Pyrx, Discovery Studio, UniProt, Protein Data Bank (PDB), PyMOL, and PubChem, Lipinski's Rule and Toxtree.

The research involved the prediction of natural compounds in red ginger with potential antipyretic properties, as well as control compounds, using relevant literature. The docking affinity binding of 10 natural compounds was determined using Pyrx software, and then the five compounds with the lowest binding affinity were docked together with the target protein and control drugs. The results of docking, in the form of protein-ligand complexes, were analyzed using Discovery Studio 16.1.0 software to better understand the systematics of the bond between proteins and ligands in a 2D scheme. To determine the oral potential of the compounds for consumption, toxicity testing, pharmacokinetics, and Lipinski’s Rule, Toxtree, and Admet-T were utilized.

**Result and Discussion**

**Target Protein Preparation and Ligan Compound**

Preparation of predicted compounds consisting of 10 compounds that have the potential to be antipyretic drug candidates. The compound is dominated using pyrx software so as to get 5 compounds with the smallest affinity bindings. The results of docking binding affinity compounds and control drugs are shown in Figure 1.

![Figure 1. Binding value affinity of ligand compounds and control compounds ibuprofen](image-url)
Interaction of Target Proteins and Ligand Compounds

Visualization of docking results using pyMOL software obtained from activeside interactions (active sites) that do not interact precisely on the same active side with each of the predicted compounds, namely (6)-shogaol, (8)-gingerol, (6)-gingerdial, gingerenone, (8)-shogaol and ibuprofen control compounds. The results of 3D visualization using pyMOL have not been able to clearly determine the interaction of these bonds, so it is continued with visualization using the Discovery Studio 2016 Client software which aims to see 2D visualizations of prediction compounds and ibuprofen control compounds. The results of the interaction between the prediction compound and the ibuprofen control compound can be seen in Figure 2.

Figure 2. Visualization of the binding position of receptor proteins and ligands, (a). (6)-shogaol; (b). (8)-gingerol; (c). (6)-gingerdial; (d). gingerenone A; (e). ibuprofen; (f). (8)-shogaol; (g). interleukin protein 10 (IL-10)

The results of the visualization of the bond between ligands and receptor proteins using Discovery studio software can be seen in Figure 3.

Figure 3. Results of 2D visualization of amino acid bond residues, (a). Interleukin 10-(6)-shogaol; (b). Interleukin 10-(8)-gingerol; (c). Interleukin 10-(6)-Gingerdiol; (d). Interleukin 10-gingerenone A; (e). Interleukin 10-(8)-shagaol; (f). Interleukin 10-Ibuprofen.
Based on the results of visualization of amino acid residual bonds, it can be seen that there are hydrogen bonds and hydrophobic bonds in each ligand. The types of bindings can be seen in Table 1.

### Table 1. Types of bond residues of amino acid compounds and ibuprofen as control compounds

<table>
<thead>
<tr>
<th>Types of compounds</th>
<th>Hydrogen bonding</th>
<th>Hydrophobic bonds</th>
</tr>
</thead>
<tbody>
<tr>
<td>(6)-shogaol</td>
<td>ASP 473</td>
<td>ILE 62, LEU 431, TRP 467, VAL 50</td>
</tr>
<tr>
<td>(8)-gingerol</td>
<td>ASP 473, THR 56</td>
<td>GLU 59, ILE 6</td>
</tr>
<tr>
<td>(6)-gingerdio</td>
<td>ASP 473</td>
<td>GLU 59, ILE 62, VAL 50</td>
</tr>
<tr>
<td>Gingerenone A</td>
<td>ASN 435</td>
<td>ASP 473, ILE 62, LEU 431, PHE 472, PRO 44</td>
</tr>
<tr>
<td>(8)-shogaol</td>
<td>HIS 434</td>
<td>HIS 75, LEU 431, PRO 443, 43</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>-</td>
<td>ASP 473, HIS 434, ILE 62, LEU 431, PRO 430, TRP 46</td>
</tr>
</tbody>
</table>

### Potential Parameters of Compounds as Biooral

Biooral potential analysis can be known from the rule of good medicine (Lipinski’s rule of five) and toxicity tests and oral bioavailability of the experimental class significantly affected the ligands’ height. This provision indicates that a compound can be categorized as potentially biooral if it can meet several predetermined rule criteria. The following is a biooral potential test using lipinsky and toxtree software.

### Table 2. Parameters Lipinsky RO5 ligands (compounds and control drugs)

<table>
<thead>
<tr>
<th>Lipinsky</th>
<th>(6) Shogaol</th>
<th>(8) gingerol</th>
<th>(6) gingerdio</th>
<th>(6) Gingerenone A</th>
<th>(8) Shogaol</th>
<th>Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>276.4</td>
<td>322.4</td>
<td>296.4</td>
<td>356.4</td>
<td>304.4</td>
<td>206.28</td>
</tr>
<tr>
<td>XlogP3</td>
<td>3.7</td>
<td>4.2</td>
<td>3</td>
<td>3.7</td>
<td>4.8</td>
<td>3.5</td>
</tr>
<tr>
<td>Hydrogen bond Donor count</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hydrogen Bond Acceptor count</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table 3. Ligand toxicity parameters with toxtree software

<table>
<thead>
<tr>
<th>Compound name</th>
<th>Toxicity test results</th>
</tr>
</thead>
<tbody>
<tr>
<td>(6)-shogaol</td>
<td>Safety</td>
</tr>
<tr>
<td>(8)-gingerol</td>
<td>Safety</td>
</tr>
<tr>
<td>(6)-gingerdio</td>
<td>Safety</td>
</tr>
<tr>
<td>gingerenone A</td>
<td>Safety</td>
</tr>
<tr>
<td>(8)-shogaol</td>
<td>Safety</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Safety</td>
</tr>
</tbody>
</table>

Tissue damage (e.g., squashed injury) can cause fever. Immunological factors such as immune complexes and lymphokine cause febrile disease in vascular collagen diseases (e.g., Systemic lupus erythematis, rheumatoid arthritis) and hypersensitivity states (e.g., drug reactions or blood transfusions). The entire substance above causes mononuclear phagocytic cells (monocytes, tissue macrophages or Kupffer cells) to make endogenous pyrogens (EP = Endogenous Pyrogen). EP is a small protein (molecular weight 20,000) similar to interleukin 10, which is an important intercellular immunoprocess mediator in the body. The EP mechanism induces fever through influence on the preoptic area in the anterior hypothalamus. EP releases arachidonates in the hypothalamus which are further converted into prostaglandins. The anterior hypothalamus contains many thermosensitive neurons. This area is also rich in serotonin and norepineprin which mediates the occurrence of fever, EP increases the concentration of these mediators. Furthermore, these two monoamines will increase cyclic adenosine monophosphate (C-AMP) and prostaglandins in the central nervous system (Prajitha et al., 2018).

The compounds gingerol and shagaol are abundant in red ginger and have been found to possess biological activity as interleukin receptor inhibitors, as indicated in Table 2. To determine the biological activity of these compounds and compare it with that of ibuprofen, the 3D structure of the target protein, interleukin 10 receptor, was prepared by selecting the protein structure in its active form, which is still bound to the ligand (Murugesan et al., 2020; Nair & Paliwal, 2021). The resulting visualization shows the interaction between amino acid residues and ligands, and the presence of amino acid interactions allows for intermediate contact...
with the interleukin 10 receptor, thereby exhibiting heat inhibition activity.

### Table 4. Results of pharmacokinetic tests of ligand compounds using Admet-Tox software

<table>
<thead>
<tr>
<th>Pharmacokinetic test</th>
<th>(6) Shogaol</th>
<th>(8) Gingerol</th>
<th>(6) Gingerdiol</th>
<th>(6) Gingerenone A</th>
<th>(8) Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption (%)</td>
<td>92.686</td>
<td>91.716</td>
<td>91.153</td>
<td>91.641</td>
<td>91.999</td>
</tr>
<tr>
<td>Distribution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VDss (L/Kg log)</td>
<td>0.501</td>
<td>0.588</td>
<td>0.615</td>
<td>0.021</td>
<td>0.559</td>
</tr>
<tr>
<td>BBB Permeability</td>
<td>-0.197</td>
<td>-0.794</td>
<td>-0.829</td>
<td>-0.366</td>
<td>-0.28</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Escretion</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Total clearance</td>
<td>1.4</td>
<td>1.4</td>
<td>1.246</td>
<td>0.205</td>
<td>1.499</td>
</tr>
<tr>
<td>Renal OCT2</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Toxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ames toxicity</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Skin sensitisation</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

The force of interaction between two or more molecules that bind reversibly is known as binding affinity (Andurkar et al., 2014). The bond energy or binding affinity between the interleukin bond and the ligand (the active compound) was compared between natural compounds and control compounds (Mai et al., 2022; Yadav et al., 2012). The docking results showed that five compounds, namely (6)-shogaol, (8)-gingerol, (6)-gingerdiol, gingenenone A, and (8)-shogaol, had the smallest binding affinity value, which was very close to that of the control compounds. The binding affinity value of ibuprofen was -7.3, which was similar to the five compounds mentioned above (Iqbal Farooqi et al., 2020). Among these compounds, (6)-shogaol exhibited the most stable binding affinity to receptor proteins, as a smaller affinity binding value indicates a better binding with the receptor. Therefore, based on the binding affinity mentioned above, the compound (6)-shogaol requires little energy to bind to the interleukin 10 protein (de Oliveira et al., 2016).

Energy binding is a crucial parameter for evaluating the strength of binding affinity between a protein and a ligand, which is determined by the energy values (Zhou, 2003). A lower energy value indicates a more stable and spontaneous bond formation, and this parameter has been widely used in drug discovery and development (Abdel-Hamid & McCluskey, 2014).

The binding site is a critical region on a protein that interacts with ligands, and it plays a vital role in regulating the protein's conformation and function. The binding site typically involves specific amino acid residues that form interactions with the ligand, such as hydrogen bonds, hydrophobic bonds, and electrostatic bonds (Kumar et al., 2018; Tsujikawa et al., 2016). These interactions between the ligand and the protein's binding site provide the driving force for the formation of a stable and specific protein-ligand complex, which is essential for biological activity.

Figure 3 reveals the presence of 6 binding amino acid residues obtained from ibuprofen tethering, including ASP 473, HIS 434, ILE 62, LEU 431, PRO 430, TRP 467. These amino acid residues serve as a reference for comparing the test ligands, namely (6)-shogaol, (8)-gingerol, (6)-gingerdiol, gingenenone A, and (8)-shagaol, with the aim of increasing the activity of interleukin receptor 10. The visualization of amino acid residue bonds between the ligands shows similarities in several bonds, particularly hydrogen bonds and hydrophobic bonds. Hydrogen bonds are considered strong because H atoms with F, O, N, and C atoms have a high electronegativity. On the other hand, nonpolar side chain bonds of neutral amino acids in proteins are relatively weak compared to hydrogen bonds (Sehgal et al., 2013; Singh et al., 2021).

The identification of these binding amino acid residues is critical in understanding how the ligands interact with the protein's binding site and, consequently, affect its biological activity. The specific interactions between the ligands and the binding site are essential in forming a stable and specific protein-ligand complex. This complex is vital for the biological activity of the protein and plays a crucial role in regulating its conformation and function. By comparing the amino acid residues found in ibuprofen tethering and the test compounds, it is possible to understand the binding mechanism and optimize drug design.
ligands, researchers can determine which compounds have the potential to increase the activity of interleukin receptor 10 and develop new drugs with improved therapeutic effects.

The results obtained from tethering experiments conducted on each compound with the interleukin 10 receptor protein exhibit a considerable degree of variability. However, a specific compound, (6)-shogaol, has demonstrated an amino acid residue bond pattern that is similar to the control compound ibuprofen. The compound (6)-shogaol binds to amino acid residues ASP 473, ILE 62, LEU 431, TRP 467, and VAL 502, with four of these residues being similar to those found in the control compound. The other residues involved in the binding, however, differ from those found in the control compound.

Moreover, the binding affinity value between ibuprofen and the natural compounds is relatively the same, which is -7.3 and 72, respectively. These findings suggest that the compounds (6)-shogaol, (8)-gingerol, (6)-gingerdial, gingenenone A, and (8)-shagaol, which were tethered using interleukin 10 receptor proteins, have the potential to be used as natural antipyretics. Further research is needed to determine the effectiveness and safety of these compounds in treating fever (Xie & Wang, 2023).

Results of biooral tests using Lipinsky RO5 and toxtree software indicate that the dodoked compound meets the criteria for being a drug that can be taken orally or by mouth according to Lipinsky RO5 rules. All the ligand compounds, including (6)-shagaol, (8)-gingerol, (6)-gingerdial, gingenenone A, and (8)-shagaol, and ibuprofen, have a molecular weight of less than 500, a LogP value of less than 5, the number of hydrogen bond donors less than or equal to 5, and the number of hydrogen bond acceptors less than or equal to 10, making them suitable for use as oral medicine.

More specifically, according to Lipinsky test data, (6)-shagaol has a molecular weight of 276.4 and a logP value of 3.7, with 1 hydrogen bound donor and 3 hydrogen bond acceptors. In comparison, ibuprofen has a molecular weight of 206.28 and a logP value of 3.5, with 1 hydrogen bond donor and 2 hydrogen bond acceptors, satisfying the Lipinsky RO5 criteria for an oral drug.

Furthermore, toxicity tests using toxtree software indicate that all six compounds, including (6)-shagaol, (8)-gingerol, (6)-gingerdial, gingenenone A, (8)-shagaol, and ibuprofen, are safe for oral consumption. These results suggest that these ligand compounds could potentially be used as natural antipyretics (da Cruz et al., 2020).

The results of the admet-T software test revealed some interesting information regarding the potential of these ligand compounds as natural antipyretics (Roy et al., 2019). In terms of pharmacokinetics, all ligands were found to be highly absorbable, with an absorption rate greater than 80% and a compound distribution value (VDss) of over 0.45. However, it was observed that gingerenone A had a lower distribution value of 0.021. Moreover, the permeability of these compounds in penetrating the blood-brain barrier was not well distributed, with a log value of BB < -1, but their distribution in the brain barrier was still effective due to their high value of >0.3.

Metabolic tests showed that all compounds can be metabolized by CYP3A4, CYP1A2, CYP2C19, and CYP2C9 enzymes, while the drug compounds cannot be metabolized by these enzymes. Additionally, excretion tests revealed that these compounds have relatively similar total permissible dose results ranging from 0.2 to 1.4 ml/min/kg under normal circumstances, and that the compounds were not renal OCT2 drugs (Satheesh et al., 2020).

Toxicity tests indicated that none of the ligands have mutagenic potential using bacteria, nor do they cause irritation to the skin or liver toxicity, which suggests that they are safe to use. Based on the results of the lipinsky, toxtree, and admet-T tests, these compounds are safe and promising drug candidates for natural antipyretics.

**Conclusion**

This research aimed to identify potential antipyretic drug candidates in red ginger using reverse docking technique targeting interleukin-10 (IL-10). The study identified two promising compounds, gingerol and shogaol, that showed similar amino acid bond residues as ibuprofen control compounds that use IL-10 receptor protein. The results indicate that (6)-shogaol has potential as an antipyretic drug, as it inhibits the action of prostaglandins by increasing the work of interleukin protein 10, making it a highly recommended candidate. Safety analysis of the compounds showed that they are safe for oral consumption, distribution, metabolism, excretion, and toxicity. This finding suggests that these compounds could be viable alternatives to synthetic antipyretic drugs that often have side effects. The potential of gingerol and shogaol as antipyretic drug candidates is significant as they are natural compounds found in red ginger. This finding presents an opportunity to develop natural antipyretic drugs that are more affordable and safer for patients. It is important to note that further research is necessary to explore the compounds’ potential in targeting other proteins to establish their efficacy as antipyretic drugs fully. Overall, this study contributes to the development of natural antipyretic drugs by providing evidence of the potential of gingerol and shogaol in red ginger. The
findings of this study have significant implications for the pharmaceutical industry and the development of alternative medicines.

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Conflicts of Interest
The authors declare no conflict of interest.

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