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Study In Silico of Gingerol and Shogaol from Red Ginger Rhizome (*Zingiber Officinale* var. rubrum) as Anti-Inflamatory

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ABSTRACT

Inflammation occurs when the enzyme *phospholipase A2* (PLA2) releases arachidonic acid from cell membranes, leading to the production of pro-inflammatory mediators. Gingerol and shogaol are bioactive compounds with anti-inflammatory properties found in red ginger (*Zingiber Officinale* var. rubrum). This research aims to investigate the potential anti-inflammatory activity of gingerol and shogaol against osteoarthritis using in silico methods. The in silico tests utilized Hyperchem 8, Chimera 1.10.1, and molecular docking was performed using AutoDock Tools, supplemented with Autogrid and Autodock 4. The results of molecular docking showed hydrogen bonds and binding energy. The binding energy values for 10-gingerol were -9.01 kcal/mol, 10-shogaol -8.85 kcal/mol, 8-shogaol -8.72 kcal/mol, and 6-gingerol -8.07 kcal/mol. The results indicate that gingerol and shogaol compounds have higher binding energies compared to the target protein *Phospholipase A2* (Sodium Diclofenac) at -7.57 kcal/mol. This suggests that gingerol and shogaol compounds from red ginger rhizome (*Zingiber Officinale* var. rubrum) have potential as anti-inflammatory agents.
Keywords: *gingerol; shogaol; anti-inflammatory; phospoliphase A2; in silico*

ABSTRAK

Inflamasi atau peradangan terjadi akibat enzim *phospoliphase A2* (PLA2) yang melepaskan asam arakidonat dari membran sel, sehingga menghasilkan mediator proinflamasi. Gingerol dan shogaol merupakan senyawa bioaktif yang memiliki kandungan antiinflamasi pada tanaman jahe merah (*Zingiber Officinale* var. rubrum). Penelitian ini bertujuan untuk mengetahui potensi aktivitas dari gingerol dan shogaol sebagai antiinflamasi terhadap penyakit osteoartritis secara in silico. Uji in silico menggunakan program Hyperchem 8, Chimera 1.10.1 dan pengujian molecular docking menggunakan program AutoDock Tools, dilengkapai dengan program (Autogrid dan Autodock 4). Hasil pengujian molecular docking adalah ikatan hidrogen dan energi ikatan. Nilai energi ikatan pada senyawa 10-gingerol sebesar -9,01 kkal/mol, 10-shogaol sebesar -8,85 kkal/mol, 8-shogaol sebesar -8,72 kkal/mol dan 6-gingerol sebesar -8,07 kkal/mol, Hasil menyatakan bahwa senyawa gingerol dan shogaol memiliki energi ikatan yang lebih besar dibandingkan dengan protein target *Phospholiphase A2* (Natrium Diclofenac) sebesar -7,57 kkal/mol. Hal ini menunjukan bahwa senyawa gingerol dan shogaol dari Rimpang Jahe Merah (*Zingiber Officinale* var. rubrum) berpotensi sebagai antiinflamasi.
Kata kunci: gingerol; shogaol; antiinflamasi; *phospoliphase A2*; *in silico*

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INTRODUCTION

Red ginger is a prolific plant native to South Asia and is widely distributed throughout the world. In Asia, particularly in Indonesia, red ginger is often used as an alternative medicine and raw material for herbal drinks [(1)]. Red ginger offers greater benefits compared to other types of ginger because its rhizomes contain essential oil reserves, including limonene, camphene, zingiberene, gingerol, and shogaol. Gingerol in red ginger causes the characteristic hot taste and is very effective as an anti-inflammatory agent for the body [(2)]. The primary components responsible for the spicy flavor in red ginger are gingerol and shogaol. The primary compounds within the red ginger rhizome are gingerol compounds, such as *6-gingerol, 8-gingerol, and 10-gingerol* [(3)]. Inflammation is a normal protective response to tissue injury caused by physical trauma, damaging chemicals, or microbiological substances. Inflammation is the body's attempt to inactivate or destroy invading organisms, remove irritants, and set the stage for tissue repair [(4)]. Ginger spice and its various phytoconstituents have the potential to reduce inflammation. In traditional Asian medicine preparations, ginger rhizomes have been used to treat mild forms of rheumatoid arthritis and osteoarthritis, aligning with these effects. Phenylpropanoids from ginger rhizomes (gingerol, shogaol) have been found to target the enzyme *phospholipase A2*, inhibiting the secretion of IL-1beta and prostanoids, thus potentially disrupting arachidonate-phospholipid remodeling [(5)]. One medicinal plant known to have anti-inflammatory effects is red ginger (*Zingiber officinale var. rubrum*), which contains active compounds such as gingerol and shogaol that play a role in inhibiting the inflammatory process. Gingerol, zingerone, and shogaol are three forms of red ginger derived from bitter, spicy, and aromatic oleoresin. It also contains anti-inflammatory oleoresin, potent antioxidants, and analgesics, which help alleviate joint pain and muscle tension by preventing the formation of prostaglandins. Based on this, the potential of gingerol content can be developed as a new anti-inflammatory drug [(6)].

Molecular docking studies can be used to predict the bioactivity of a compound before conducting laboratory experiments. The advantages of this method include reducing the use of experimental animals, equipment, materials, and costs, as well as visualizing the ligand's mechanism of action on its target and optimizing the ligand's compound structure [(7)]. The program used for docking ligands with their target proteins is AutoDock Tools 1.5.7. AutoDock 4 consists of two main programs: AutoDock4 and AutoGrid. Based on the literature review regarding *molecular docking* from previous research, this study will conduct *molecular docking* to determine the potential of gingerol and shogaol from red ginger rhizome (*Zingiber Officinale var. rubrum*) as anti-inflammatory agents for osteoarthritis by inhibiting the *phospholipase A2* (PLA2) enzyme by in silico.

MATERIALS AND METHODS

MATERIALS

The 3D structures of the bioactive compounds gingerol and shogaol can be downloaded from website https://pubchem.ncbi.nlm.nih.gov/. The structure of the target protein *phospholipase A2* (PDB ID: 2B17) can be downloaded from the Protein Data Bank (PDB) website at http://www.rcsb.org/pdb/home/home.do. The Materials and Methods section includes the following components: research design, research procedures, sampling method, and data analysis method.

METHODS

a. Optimization of the 3D Structures of Gingerol and Shogaol Compounds

The 3D structures of the gingerol and shogaol compounds were optimized using the Hyperchem 8 program. The optimization was performed using the semi-empirical AM1 (Austin Model 1) computational method, and *single point* calculations and geometry optimization were carried out.

b. Preparation of the 3D Structure of the Target Protein *Phospholipase A*

Protein preparation was performed using the Chimera 1.10.1 program by separating the 3D structure of the Phospholipase A2 protein from its native ligand.

c. Validation of the *Molecular Docking* Method

The validation of the *molecular docking* method was performed using Autodock Tools (Autodock 4 and Autogrid) by re-docking the native ligand to the *phospholipase A2* protein
From which its native ligand had been removed. The validation parameter for the *molecular docking* method is the Root Mean Square Deviation (RMSD) value. The docking method is considered valid if the RMSD value is ≤3 Å, which means that the docking parameters used are valid and can be used subsequently for docking the test compounds [8]

d. Docking of Gingerol and Shogaol to the *Phospholipase A2* Protein

The optimized gingerol and shogaol compounds were subsequently docked to the *phospholipase A2* protein, from which its native ligand had been removed, using the Autodock Tools application with the same docking procedure as during the method validation using the native ligand. The analysis results reveal the binding conformation of the compounds to the protein, along with their binding energy values and the hydrogen bonds formed.

e. Data Analysis

The results from the *molecular docking* process are the binding energy and the hydrogen bonds formed. Binding energy is used to indicate the strength of the bond between the compound and the protein. The lower the binding energy value, the stronger and more stable the bond formed. Meanwhile, the types of hydrogen bonds are used to analyze the interaction mechanisms that are formed.

RESULTS AND DISCUSSIONS

a. Optimization of the 3D Structures of Gingerol and Shogaol Compounds

The downloaded 3D structures of the gingerol and shogaol compounds were optimized using the Hyperchem 8 program with the semi-empirical AM1 computational method. The optimization steps included single-point calculations and geometry optimizations to obtain the most stable structures of the gingerol and shogaol compounds. In the semi-empirical method, a simplification of the two-electron integrals of the Hamiltonian is performed. The success of the compound optimization is indicated by the total energy resulting from geometry optimization being lower than that from the single-point calculation. The optimization results for the gingerol and shogaol compounds are shown in Figure 1.

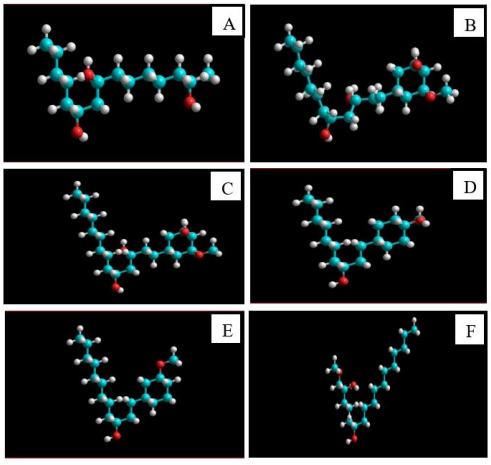

Figure 1. Optimization Results of the 3D Structures of Gingerol and Shogaol Compounds

The total energy values from the single point calculations and geometry optimizations obtained for the gingerol and shogaol compounds were as follows: for 6-gingerol, -4682.1934 kcal/mol and -5180.0640 kcal/mol, respectively; for 8-gingerol, -5651.7561 kcal/mol and -5746.5419 kcal/mol; for 10-gingerol, -6213.7397 kcal/mol and -6310.4090 kcal/mol; for 6-shogaol, -4979.9553 kcal/mol and -5084.9439 kcal/mol; for 8-shogaol, -5551.5017 kcal/mol and -5648.3059 kcal/mol; and 10-shogaol, -6113.4146 kcal/mol and -6208.5909 kcal/mol. Based on these results, the optimized structures of the gingerol and shogaol compounds were obtained**.**

b. Preparation of *Phospholipase A2* Protein

The *Phospholipase A2* (PLA2) protein was prepared by separating the target protein from its native ligand using the Chimera 1.10.1 program, resulting in a protein structure without the native ligand and a separate native ligand structure, as shown in Figure 2. The separation of the protein from its native ligand aims to provide a binding pocket for the test compounds to interact with the PLA2 protein. In the PLA2 target protein, there is only 1 chain A that will be used for the docking process, and the native ligand present in chain A is the native ligand (DIF). The next step is to remove all native ligands not used in the docking process, including the removal of water molecules (H2O) attached to the target protein. The purpose of removing these water molecules is to prevent them from interfering with the docking process, ensuring that only amino acids in the target protein interact with the test compound [10].

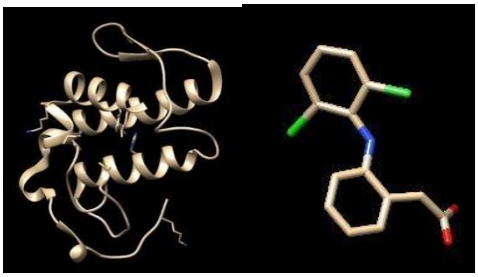

Figure 2. Structure of PLA2 Protein without Ligand (a) and Native Ligand (b)

c. Validation of the *Molecular Docking* Method

The validation of the *molecular docking* method was performed using the AutoDockTools 1.5.7 program with the redocking method (re-docking) of the native ligand of the PLA2 protein with the prepared macromolecule. The parameter used was the Root Mean Square Deviation (RMSD). The results obtained in this process are the grid box parameters and the RMSD value [9].

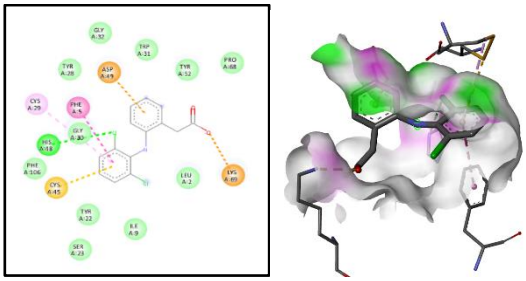

Figure 3. Visualization of the 2D (a) and 3D (b) interactions of the PLA2 protein with its native ligand

c. Docking of Gingerol and Shogaol to the *Phospholipase A2* Protein

The docking process between the target protein and the native ligand, along with the gingerol and shogaol compounds, produces 10 conformations with the lowest to highest binding energies, as listed in the (.dlg) format. Each conformation forms hydrogen bonds between the gingerol and shogaol compounds and their amino acid residues.

A low binding energy value indicates a stable protein-ligand complex. A positive binding energy value indicates that a system has little or no reaction potential, so bonds are not formed [(11)]. The binding energy in molecular docking can illustrate the interaction and affinity between gingerol and shogaol compounds and the target protein, the phospholiphase A2 enzyme. In addition to bond energy, there are also hydrogen bonds that interact with the gingerol and shogaol compounds. The docking results between the target protein, the phospholiphase A2 enzyme, and the native ligand and gingerol and shogaol compounds can be seen in the table 1.

Tabel 1. Docking Results of Gingerol and Shogaol Compounds with the Native Ligand on PLA2 Protein

Protein Target	Ligan	Energi Ikatan (Kkal/mol)	Ikatan Hidrogen
PLA2 (2B17)	***Native ligand***	**-7,57**	**HIS48**
	6-gingerol	**-8,07**	**GLY30 TYR22**
	8-gingerol	**-6,09**	**HIS48 LYS69 TYR22**
	10-gingerol	**-9,01**	**CYS29 HIS48 CYS45 TYR22**
	6-shogaol	**-7,65**	**CYS45**
	8-shogaol	**-8,72**	**LYS69 CYS45 HIS48**
	10-shogaol	**-8,85**	**CYS45**

Based on the docking results obtained, it can be described that the affinity energy indicates the strength of the interaction between the test ligand and the target protein, the phospholipase A2 enzyme. The lower the binding affinity of gingerol and shogaol compounds, the stronger the interaction between the ligand and the protein, potentially increasing the ligand's effectiveness as an inhibitor of the target enzyme [(12)]. The binding energy value for 10-gingerol was -9.01 kcal/mol, 10-shogaol was -8.85 kcal/mol, 8-shogaol was -8.72 kcal/mol, and 6-gingerol was -8.07 kcal/mol. The results indicate that gingerol and shogaol compounds have higher binding energies compared to their native ligand (diclofenac), which has a value of -7.57 kcal/mol. Research by [3] found a binding energy of -8.2 kcal/mol for the 6-gingerol compound, which is lower than the binding energy of -8.7 kcal/mol for the 6-gingerol compound in this study. This indicates that gingerol and shogaol compounds from red ginger rhizome (*Zingiber officinale* var. rubrum) can inhibit the phospholiphase A2 enzyme and have potential as anti-inflammatory drugs

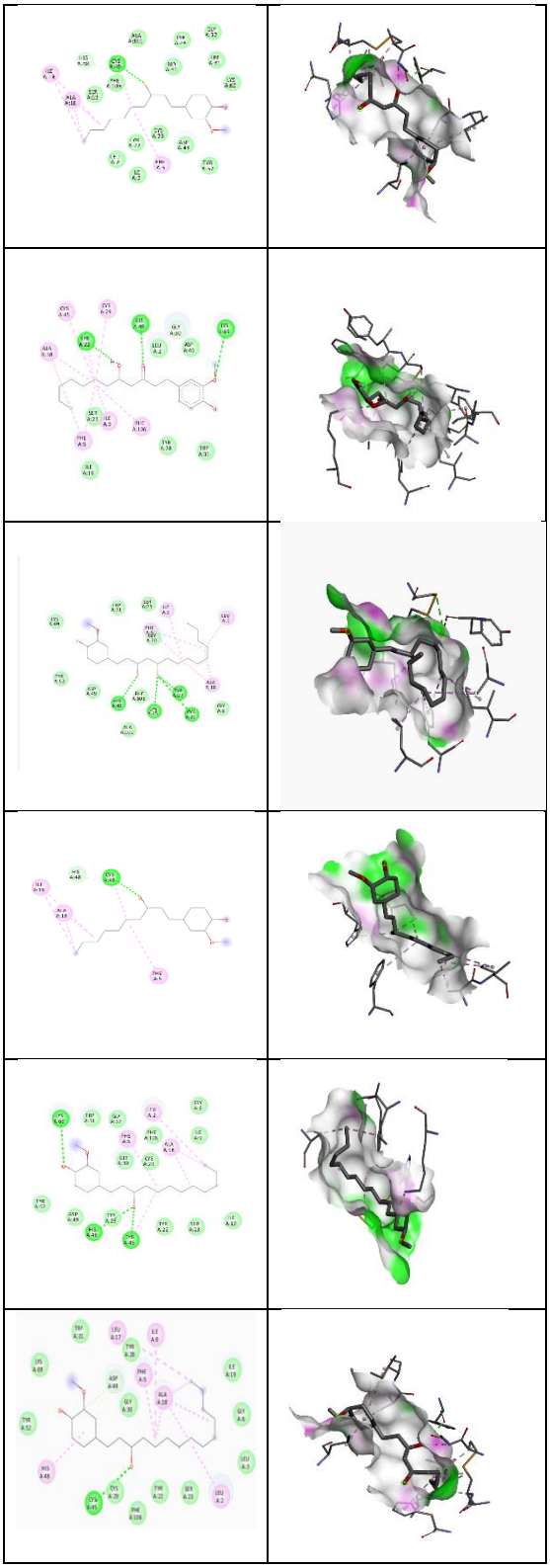

Figure 4. Visualitation of the 2D and 3D Interaction Result of Docking Gingerol and Shogaol Compounds to the PLA2 Protein

Based on the comparison of binding energies in this study, it can be seen that the affinity of gingerol and shogaol compounds for the target protein of the phospholiphase A2 enzyme has a good binding energy value and can be seen from the strength of the energy produced compared to its native ligand. The smaller (more negative) the bond energy, the more stable (stronger) the resulting bond (protein

and ligand complex) so that the contact time of the ligand with the receptor is longer [14]. In addition to bond energy, ligand-protein interaction is an important indicator in comparing the ability of a test ligand to replace a natural ligand as an inhibitor. Interaction between a compound and a protein can occur through the formation of hydrogen bonds between them. Hydrogen bonds formed at specific locations allow for reactions between enzymes and substrates. This suggests that if a compound is able to bind to a protein at a location similar to that of the substrate, then the compound has the potential to have a similar mechanism of action to the substrate [13]. The presence of hydrogen bonds is often used as a primary indicator in docking score assessments. Types of chemical interactions that can occur as a result of the docking process include hydrogen bonds, hydrophobic interactions, and van der Waals interactions. Hydrogen bonds form between hydrogen atoms in one molecule and atoms in another molecule with higher electronegativity. These bonds are among the strongest intermolecular bonds and have a high degree of stability [15]. The conventional hydrogen bond is one of the strongest non-covalent interactions. This interaction can play a vital role in various processes, including the stability and affinity between two molecules.

CONCLUSIONS

Based on the research result, it can be conclude that the affinity of several derivatives

of gingerol and shogaol compounds have highter binding energy values compared to its native ligand, which has a value of -7,5 kcal/mol on the target protein *phospholipase A2* enzyme. Gingerol and shogaol compounds inhibit the *phospholipase A2* (PLA2) enzyme, acting as anti-inflammatory agents

REFERENCE

1. Priscinya Christiana Debora A, Ayu Pratama A, Ambarati T, Granadha S, Nuriah S, Ilmu Kesehatan F, et al. Review Artikel: Efektivitas Senyawa Antiinflamasi Dan Antibakteri Pada Rimpang Jahe (Zingiber officinale R.). 2022;19–29.
2. Masniah M, Rezi J, Faisal AP. Isolasi Senyawa Aktif Dan Uji Aktivitas Ekstrak Jahe Merah (Zingiber Officinale) Sebagai Imunomodulator. J Ris Kefarmasian Indones. 2021;3(2):77–91.
3. Mao QQ, Xu XY, Cao SY, Gan RY, Corke H, Beta T, et al. Bioactive compounds and bioactivities of ginger (zingiber officinale roscoe). Foods. 2019;8(6):1–21.
4. Garakia CSH, Sangi M, Koleangan HSJ. Uji Aktivitas Antiinflamasi Ekstrak Etanol Tanaman Patah Tulang (Euphorbia tirucalli L.). J MIPA. 2020;9(2):60.
5. Matin M, Joshi T, Wang D, Tzvetkov NT, Matin F Bin, Wierzbicka A, et al. Effects of Ginger (Zingiber officinale) on the Hallmarks of Aging. Biomolecules. 2024;14(8):1–37.
6. Akmal Syihabuddin, Taufik Muhammad Fakih, Dwi Syah Fitra Ramadhan. Pengembangan Obat Baru dari Senyawa Curcumin, Genistein, Lactacystin, Phloretin, Quercetin sebagai Inhibitor RNA Polimerase MTB dengan Menggunakan Metode In Silico. Bandung Conf Ser Pharm. 2022;2(2):1062–70.
7. Pharmacia J, Waluya M, Pharmacia J, Waluya M, No V, Zulfa T, et al. Studi Molecular Docking Senyawa Kimia dari Herba Putri Malu (Mimosa pudica) Terhadap Inhibisi Enzim A-Glukosidase Sebagai Antidiabetes Melitus A Study Of The Molecular Docking of Chemical Compounds From The Mimosa Herb (Mimosa pudica) on The α -Glucos. 2024;3(4).
8. Muttaqin FZ. Studi Molecular Docking, Molecular Dynamic, Dan Prediksi Toksisitas Senyawa Turunan Alkaloid Naftiridin Sebagai Inhibitor Protein Kasein Kinase 2-A Pada Kanker Leukemia. Pharmacoscript. 2019;2(1):49–64.
9. Vitadella V, Bulan CP, Sinurphospat JAN, Latief M, Yusnaidar Y, Tarigan IL.

Studi In Silico Senyawa Bioaktif Daun Miana (Coleus scutellariodes (L). Benth) sebagai Inhibitor Enzim Asetikolineterase (Ache) pada Alzheimer. J Sains dan Kesehat. 2024;6(2):282–91.
10. Ni Luh Ari Krisma Anjani and Ni Putu Linda Laksmiani, “Potensi Isokuersitrin Sebagai Agen Antihiperpigmentasi Secara In Silico Dengan Metode Molecular Docking,” *Pros. Work. dan Semin. Nas. Farm.*, vol. 1, no. September, pp. 171–181, 2023, doi: 10.24843/wsnf.2022.v01.i01.p14.
11. Ni Made Rita Wiantini and Ni Putu Linda Laksmiani, “Studi Potensi Senyawa Hesperidin dan Naringin Kulit Jeruk Nipis (Citrus aurantifolia) sebagai Agen Antiphotoaging secara In Silico,” *Pros. Work. dan Semin. Nas. Farm.*, vol. 1, no. September, pp. 268–282, 2023, doi: 10.24843/wsnf.2022.v01.i01.p22.
12. S. Amin, S. Sabila, and H. Nur Shaleha, “Studi In Silico Interaksi Senyawa Bioaktif dari Jahe (Zingiber officinale Roscoe) sebagai Inhibitor Proton Pump dalam Terapi Asam Lambung Journal of Innovative and Creativity Studi In Silico Interaksi Senyawa Bioaktif dari Jahe (Zingiber officinale Roscoe) sebagai Inhibitor Proton Pump dalam Terapi Asam Lambung,” *J. Innov. Creat.*, vol. 1, no. 1, pp. 75–83, 2025.
13. T. Z. A. D. Putri, R. P. Findrayani, M. Isrul, and N. Lolok, “Studi Molecular Docking Senyawa Kimia Dari Herba Putri Malu (Mimosa pudica) Terhadap Inhibisi Enzim A-Glukosidase Sebagai Antidiabetes Melitus,” *J. Pharm. Mandala Waluya*, vol. 3, no. 4, pp. 225–233, 2024, doi: 10.54883/jpmw.v3i4.104.
14. H. Y. S. Iksen, “Studi In Silico Senyawa Bahan Alam Terhadap Biomarker Pembelahan Sel Kanker,” *Herb. Med. J.*, vol. 8, no. e-ISSN 2621-2625, pp. 27–33, 2025.
15. F. Ekawasti, S. Sa’diah, U. Cahyaningsih, N. L. P. I. Dharmayanti, and D. T. Subekti, “474Molecular Docking Senyawa Jahe Merahdan Kunyit pada Dense Granules Protein-1Toxoplasma gondii dengan Metode In Silico,” *J. Vet.*, vol. 22, no. 4, pp. 474–484, 2021, doi: 10.19087/jveteriner.2021.22.4.474.