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Original Article

Potential of polyether ionophore compounds as antimalarials through inhibition on *Plasmodium falciparum* glutathione S-transferase by molecular docking studies

[Potencial de los compuestos ionóforos de poliéter como antimaláricos mediante la inhibición de glutatión S-transferasa de *Plasmodium falciparum* a través de estudios de acoplamiento molecular]

Alfian Wika Cahyono[1,2], Icha Farihah Deniyati Faratisha[1], Nabila Erina Erwan[1,3], Rivo Yudhinata Brian Nugraha[1,4], Ajeng Maharani Putri[1,3], Loeki Enggar Fitri[1,4]*

[1]Malaria Research Group, Faculty of Medicine, Universitas Brawijaya, Malang, East Java, 65145, Indonesia.
[2]Doctoral Program in Medical Science, Faculty of Medicine, Universitas Brawijaya, Malang, East Java, 65145, Indonesia.
[3]Master Program in Biomedical Science, Faculty of Medicine, Universitas Brawijaya, Malang, East Java, 65145, Indonesia.
[4]Department of Parasitology, Faculty of Medicine, Universitas Brawijaya, Malang, East Java, 65145, Indonesia.
*E-mail: lukief@ub.ac.id

Abstract

Context: Malaria is still a serious global health problem due to the development of drug resistance. It is necessary to find new drugs with renewable mechanisms that are effective in killing parasites. Our previous research has analyzed more than one compound of polyether ionophore group in ethyl acetate *Streptomyces hygroscopicus* subsp. *hygroscopicus* extract. Polyether ionophore is known to have a similar mechanism of action to chloroquine which is potent in inhibiting *Plasmodium falciparum* glutathione S-transferase (PfGST).

Aims: To evaluate the potential effect of polyether ionophore toward PfGST as a target protein through molecular docking.

Methods: PfGST was obtained from Protein Data Bank. Test ligands (polyether ionophore) and control ligands (chloroquine) were obtained from PubChem. Pharmacokinetic analysis was done using SwissADME, molecular docking using PyRx 0.9, visualization using LigPlot and PyMOL, and molecular dynamics using YASARA for the best ligand activity.

Results: Lenoremycin had the highest binding affinity to PfGST (-8.53 kcal/mol) among other polyether ionophores, and nigericin had the best residue bonding with hydrophobic and hydrogen with a binding affinity of -8.25 kcal/mol compared to chloroquine complex in molecular docking and molecular dynamic simulation.

Conclusions: Polyether ionophore could serve as an antimalarial agent better than chloroquine, with nigericin as the best compound candidate in inhibiting PfGST compared to other polyether ionophores.

Keywords: malaria; molecular docking; PfGST; polyether ionophore; *Streptomyces hygroscopicus*.

Resumen

Contexto: La malaria sigue siendo un grave problema sanitario mundial debido al desarrollo de resistencia a los fármacos. Es necesario encontrar nuevos fármacos con mecanismos renovables que sean eficaces para matar a los parásitos. Nuestra investigación anterior ha analizado más de un compuesto del grupo ionóforo poliéter en el extracto de acetato de etilo de *Streptomyces hygroscopicus* subsp. *hygroscopicus*. Se sabe que el poliéter ionóforo tiene un mecanismo de acción similar al de la cloroquina, que es potente inhibidor de gutatión S-transferasa de *Plasmodiun falciparum* (PfGST).

Objetivos: Evaluar el efecto potencial del poliéter ionóforo hacia la PfGST como proteína diana a través del acoplamiento molecular.

Métodos: PfGST se obtuvo del Banco de Datos de Proteínas. Los ligandos de prueba (poliéter ionóforo) y los ligandos de control (cloroquina) se obtuvieron de PubChem. El análisis farmacocinético se realizó con SwissADME, el acoplamiento molecular con PyRx 0.9, la visualización con LigPlot y PyMOL, y la dinámica molecular con YASARA para la mejor actividad del ligando.

Resultados: La lenoremycina tuvo la mayor afinidad de unión a PfGST (-8,53 kcal/mol) entre otros poliéteres ionóforos, y la nigericina tuvo la mejor unión de residuos con hidrófobos e hidrógenos con una afinidad de unión de -8,25 kcal/mol en comparación con el complejo de cloroquina en el acoplamiento molecular y la simulación dinámica molecular.

Conclusiones: El ionóforo poliéter podría servir como agente antimalárico mejor que la cloroquina, siendo la nigericina el mejor candidato para inhibir el PfGST en comparación con otros ionóforos poliéter.

Palabras Clave: acoplamiento molecular; ionóforo poliéter; malaria; PfGST; *Streptomyces hygroscopicus*.

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AUTHOR INFO
ORCID: 0000-0002-9279-1764 (AWC) 0000-0002-4314-6961 (RYBN)
0000-0002-6767-5577 (IFDF) 0000-0001-6142-0744 (AMP)
0000-0001-9028-9861 (NEE) 0000-0002-4880-1048 (LEF)

INTRODUCTION

Malaria is still to be considered a public health problem due to its major morbidity and mortality. There were 229 million cases of malaria in the world in 2019, with the highest morbidity rates occurring in Africa (94%), Southeast Asia (3%), and the Eastern Mediterranean (3%) distributed in 87 malaria-endemic countries (World Health Organization, 2020). The high resistance to antimalarial drugs is currently a burden and a challenge for global health, so efforts are needed in drug development and discovery (Hartuti et al., 2018; Raphemot et al., 2016).

Secondary metabolites of *Streptomyces hygroscopicus* have many benefits, including antibiotic and antimalarial agents (Fitri et al., 2019; Rivo et al., 2013). Through LC-MS instrumentation, several compounds from *Streptomyces hygroscopicus* have successfully been detected as polyether ionophore groups. The polyether ionophore group is a coccidiosis prophylactic agent in animal husbandry (Rutkowski and Brzezinski, 2013). However, several studies have shown that this compound has the potential as an antimalarial agent (Kevin II et al., 2009).

Some researchers believe that the mechanism of action of the polyether ionophore is similar to that of chloroquine (Adovelande and Schrével, 1996). Through the exchange of cation transport to the cell membrane, polyether ionophores can increase the alkalinization of food vacuoles and inhibit protein degradation in lysosomes. However, the similar mechanism of action between polyether and chloroquine is still doubted by some others (Gumila et al., 1997).

Plasmodium falciparum glutathione S-transferase (PfGST) is a protein known to be a target for malaria therapy. This target is also known to be inhibited by chloroquine and various other inhibitors (Harwaldt et al., 2002). The role of PfGST in the process of detoxification and protection is very important for the survival of the parasite (Liebau et al., 2002; Perbandt et al., 2015). With this rationale in mind, this research was conducted to measure the interaction ability between polyether ionophore compounds as antimalarial agents against PfGST through a molecular docking approach.

MATERIAL AND METHODS

Streptomyces hygroscopicus subsp. *hygroscopicus* characteristics

Isolate *Streptomyces hygroscopicus* subsp. *hygorscopicus,* which has been characterized, was obtained from the Microbiology LIPI Microbial Collection (LIPI-MC) Cibinong. Furthermore, it has been subcultured in the Microbiology Laboratory, Faculty of Medicine, Universitas Brawijaya. *Streptomyces* bacteria was identified based on colony morphology and microscopic morphology through Gram staining.

Liquid chromatography-mass spectrometry (LC-MS) analysis

The crude extract of *S. hygroscopicus* was analyzed using LC-MS. This analysis was carried out under conditions according to the Shimadzu LCMS – 8040 LC-MS model, using a Shim Pack FC-ODS column (2 mm D × 150 mm, 3 m), with an injection volume of 1 µL, and the flow gradient 0/0 at 0 min, 15/85 at 5 min, 20/80 at 20 min, 90/10 at 24 min using a flow rate of 0.5 mL/min. The solvent used 90% methanol with water, the ionization was ESI, and the running time was 80 min.

The mass-to-change ratio (m/z) and the percentage abundance (% abundance) were used to analyze the LC-MS data. By looking at the total ion chromatogram, compounds were identified based on their molecular weight and retention time (RT) peaks. Compounds identified as having antimalarial activity through literature studies were selected for further analysis.

Ligand preparation

The two-dimensional structure of the polyether ionophore compound was downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and saved in the .sdf extension. Furthermore, the conversion of two-dimensional structures into three-dimensional and energy minimization using OpenBabel. The control ligand in this study was the antimalarial drug chloroquine.

Pharmacokinetic profile

The test ligands of each polyether ionophore compound were analyzed for pharmacokinetic profiles using SwissADME (http://www.swissadme.ch/) by entering the SMILES of each compound.

Receptor preparation

The target protein *Plasmodium falciparum* glutathione S-transferase (PDB ID: 1Q4J) was downloaded from the Protein Data Bank (https://www.rscb.org) and then optimized by removing any residues such as water, crystallized ligands, and cofactors using PyMOL. The structure was saved in the .pdb file extension.

Table 1. Molecular docking coordinate.

Center_X	Center_Y	Center_Z	Size_X (Å)	Size_Y (Å)	Size_Z (Å)
3.231	10.921	-3.002	30	30	30

Specific docking

The ligands from the test compound polyether ionophore and control ligands were subjected to specific molecular docking of the target protein PfGST with the following coordinates in Table 1.

Interaction visualizations

The molecular docking results are then visualized for interactions, both two-dimensional and three-dimensional, using LigPlot and PyMOL.

The molecular dynamic of PfGST

The molecular dynamic (MD) of the PfGST-test ligand complex was examined by YASARA for 50 ns compared to the PfGST-control ligand complex. The MD was run under the following conditions: pH 7.4, 298 K, and Forcefield AMBER14.

Data analysis

Several steps were carried out in this data analysis process, including analysis of the Lipinski Rule of Five's drug-likeness criteria is used to determine whether polyether ionophore compounds can be administered orally as a drug, molecular docking to evaluate the affinity of each polyether ionophore compound toward the target, and the binding interactions to compare the similarity between polyether ionophore compounds and the control ligand. After that, the polyether ionophore compound with the highest binding affinity and most bond formation compared to the control will be assessed for the molecular dynamic simulation. This analysis process aimed to assess which polyether ionophore compound was the most strongly and similarly bound to the target when compared to the control.

RESULTS

Preparation and pharmacokinetic analysis of ligands

The compound was selected in the docking analysis based on the highest intensity of the compound in the LC-MS results and is known to have antimalarial activity. The compound of the polyether ionophore group was chosen because it is a compound with fairly high intensity in the LC-MS results that have been shown to be active in inhibiting the growth of *Plasmodium falciparum* 3D7 *in vitro*. Based on the literature, polyether ionophores have been known to have antimalarial activity (Kevin II et al., 2009). The test ligands for polyether ionophore compounds were detected through LC-MS analyses from *Streptomyces hygroscopicus* subsp. *hygroscopicus* extract was prepared by taking data from PubChem, as shown in Fig. 1.

Polyether ionophore shares the similarity in the richness of oxygen atoms (Fig. 1). The oxygen atoms are present at many sites in a variety of functional groups. These compounds are also known as carboxylic ionophores due to the presence of the carboxyl group in their structures (Huczyński, 2012).

The results of the pharmacokinetic analysis of the polyether ionophore compounds using SwissADME are shown in Table 2. Based on the Lipinski Rule of Five, all polyether ionophore compound molecular weight is more than 500 mg/dL (should be <500 mg/dL), all lipophilicity (clogP) is less than 5 except lenoremycin (should be <5), hydrogen donor in all compounds is less than 5 (should be < 5), and hydrogen bond acceptor is more than 10 (should be <5)

Molecular docking

All polyether ionophore compounds showed a higher binding affinity than the control ligand (chloroquine). Lenoremycin has the highest binding affinity of -8.53 compared to control ligands and other polyether ionophores, as shown in Fig. 2.

Amino acid/protein interaction between chloroquine with PfGST showed hydrogen bond at Gly14 and hydrophobic interactions at Asn112, His107, Asn167, Leu18, Phe100, Gln104, Lys15, Tyr108, and Asn111 (Fig. 3).

Lenoremycin has the highest binding affinity, but its interaction is not specific to the control ligand site area, compared to other test ligands against PfGST (Fig. 4). The residue of the lenoremycin interaction only occurred in the hydrophobic interaction of Asn11 (Table 3). While other compounds have better residue interactions than lenoremycin. Nigericin showed good residual interaction with high binding affinity in the specific area of control ligands against PfGST.

A comparison of the interaction of test ligand residues with control ligands on PfGST (Table 3) showed that nigericin is a compound that has hydrogen bond

residues (Gly14, His107) and hydrophobic interactions (Asn111, Tyr108, Lys15, Gln104, Phe100, Asn167) with a good binding affinity (-8.25 kcal/mol). Even though lenoremycin has the highest binding affinity (-8.53 kcal/mol), the residue interactions did not show similar interactions to the control ligand (only Asn111). Other polyether ionophores with lower binding affinity also showed interaction with PfGST through hydrophobic interaction as well as hydrogen bonds. Compared to the control, carriomycin, dianemycin, septamycin, etheromycin interact with PfGST through 9, 8, 7, and 4 the same amino acid residues, respectively.

Molecular dynamic simulation

Nigericin has shown the highest binding affinity and most similar bond formation compared to the control was examined for molecular dynamic simulation. Fig. 5 shows the comparison between the PfGST-nigericin complex and the PfGST-chloroquine complex.

In molecular dynamics, any inhibition in protein caused by ligand binding can be measured by calculating the root mean square deviation (RMSD) (Abkar et al., 2021). The RMSD value of the ligand complex against PfGST showed that nigericin was higher than chloroquine (2.80 ± 0.33 vs. 2.61 ± 0.1 Å) with the RMSD value of nigericin-PfGST complex 0.5-2.8 Å and chloroquine-PfGST complex 0.5-2.6 Å, this shows stable protein-ligand complex (Fig. 5A). Furthermore, the stability of the ligand binding to the protein was continued by monitoring the conformational ligand tone. The results showed that the PfGST-chloroquine interaction was stable at 30-50 ns, nigericin-PfGST interaction was stable at 15-32 ns (Fig. 5B). In the RMSD ligand movement results, nigericin-PfGST showed better interaction stability compared to chloroquine, this was indicated by the RMSD value between 2.0-4.0 Å at least up to 30 ns with minimal fluctuation with the RMSD ligand movement nigericin value lower than chloroquine (Fig. 5C)

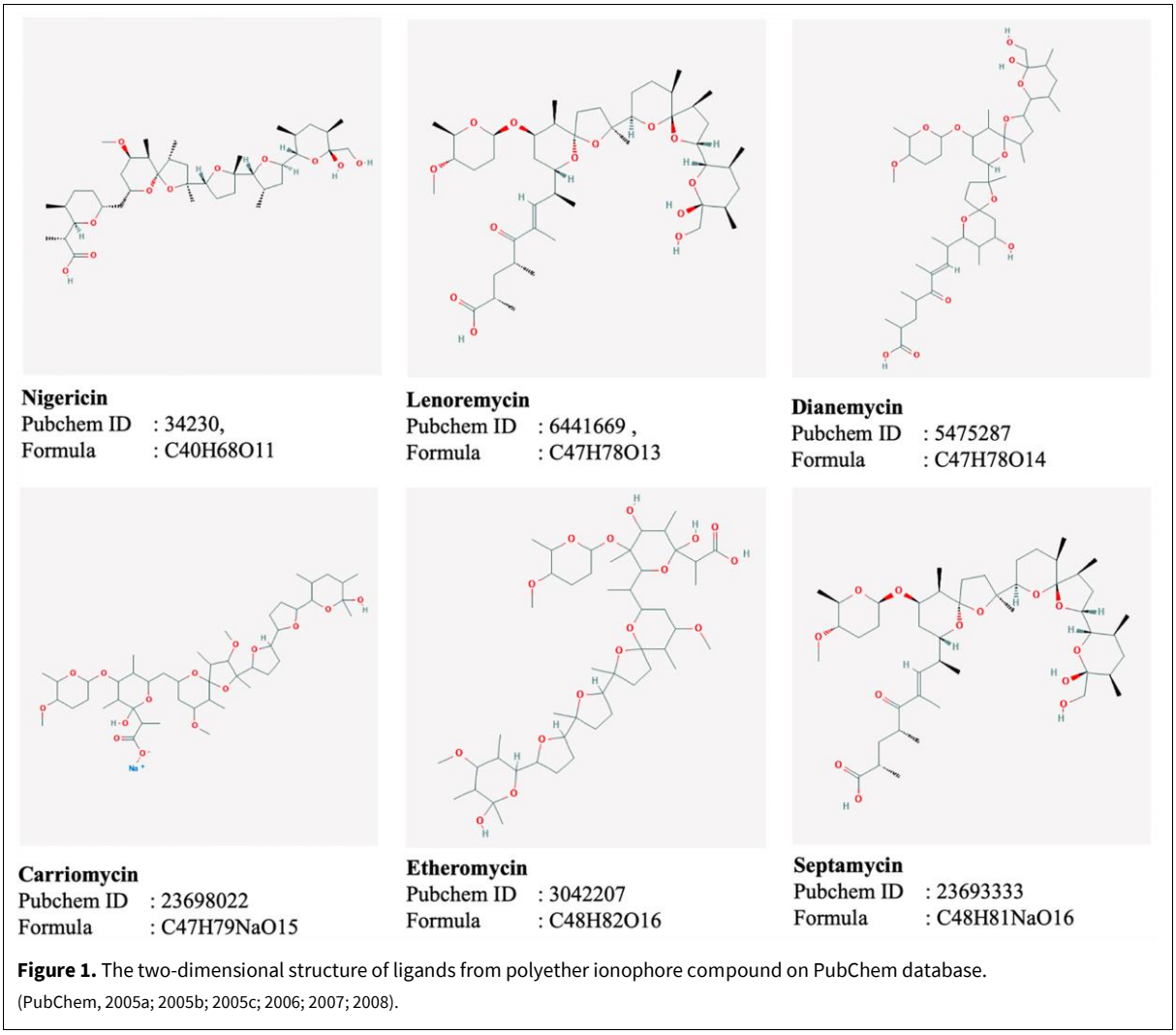
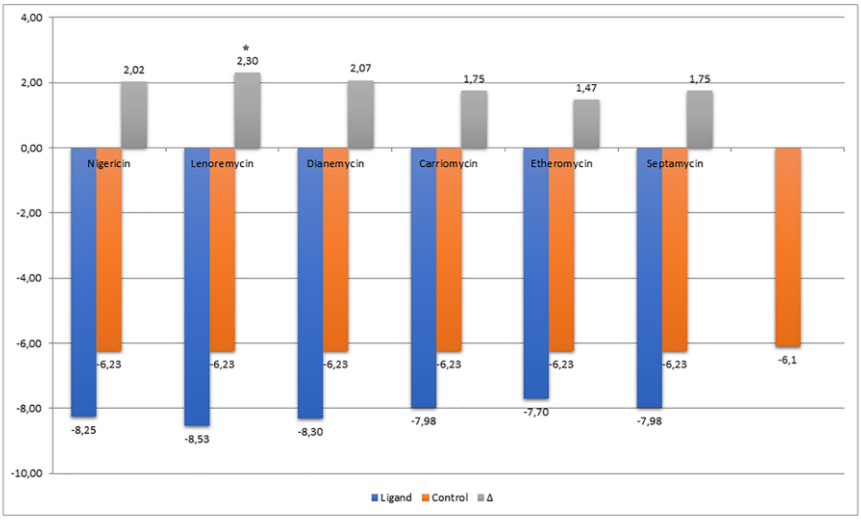


Figure 1. The two-dimensional structure of ligands from polyether ionophore compound on PubChem database. (PubChem, 2005a; 2005b; 2005c; 2006; 2007; 2008).

Table 2. Pharmacokinetic profile of polyether ionophore compounds.

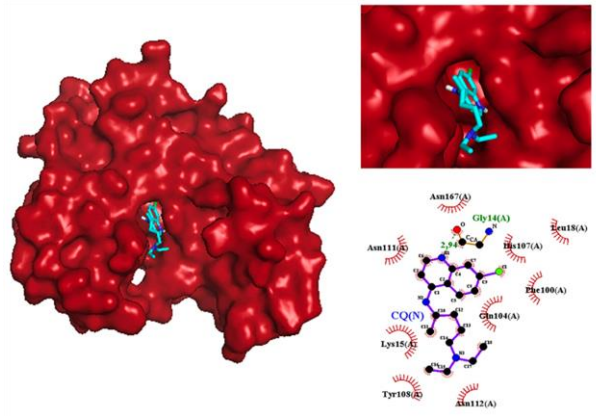
Compound names	Molecular formula	Molecular weight (g/mol)	Hydrogen bond donor	Hydrogen bond acceptor	cLogP	Lipinski criteria
Nigericin	C40H68O11	724.96	3	11	4.57	No
Lenoremycin	C47H78O13	851.11	3	13	5.62	No
Dianemycin	C47H78O14	867.11	4	14	4.88	No
Carriomycin	C47H79O15	907.11	2	15	2.03	No
Etheromycin	C48H82O16	915.16	4	16	4.28	No
Septamycin	C48H81NaO16	937.14	2	16	1.47	No



Compound Name	Binding Affinity (kcal/mol)
Chloroquine	-6.1
Nigericin	-8.25
Lenoremycin	-8.53
Dianemycin	-8.30
Carriomycin	-7.98
Etheromycin	-7.70
Septamycin	-7.98

Figure 2. The results of the binding affinity of the test and control ligand complexes for PfGST.

Molecular docking of polyether ionophore compounds (ligands in the blue bar, consisted of nigericin, lenoremycin, dianemycin, carriomycin, etheromycin, septamycin) and chloroquine as control ligand (control ligand in the orange bar). The gray bar shows the difference in binding affinity between the two ligands (test and control ligands), asterix indicates the highest and most negative binding affinity difference.



Protein Interaction of Chloroquine with PfGST	
Hydrogen Bond	Gly14
Hydrophobic Interaction	Asn112, His107, Asn167, Leu18, Phe100, Gln104, Lys15, Tyr108, Asn111

Figure 3. Visualization of chloroquine as a control ligand (light blue) with PfGST (red).

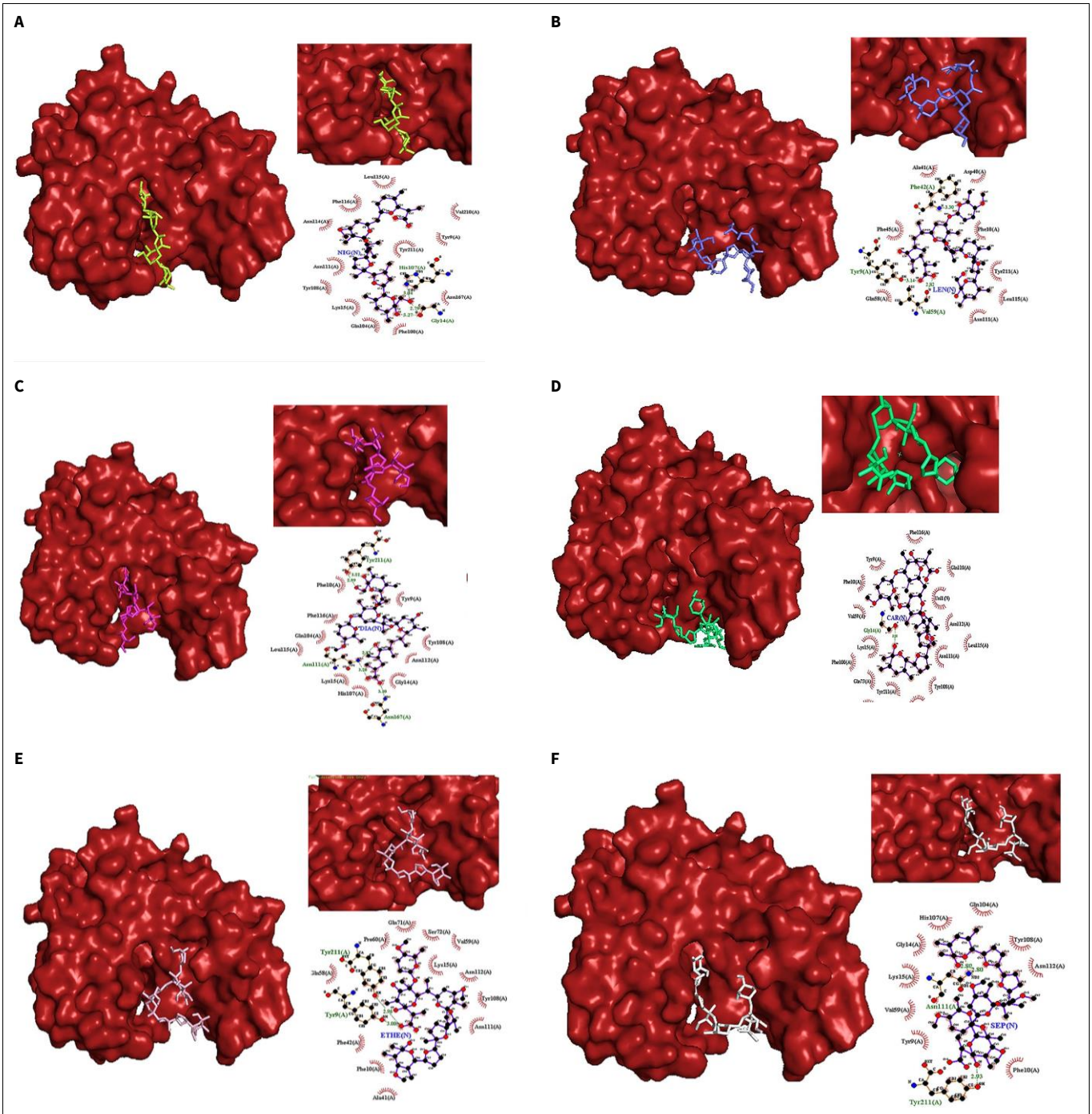


Figure 4. Visualization of the interaction of the test ligand against PfGST.

(A) Interaction of nigericin (yellow) with PfGST (red); **(B)** Interaction of lenoremycin (blue) with PfGST (red); **(C)** Interaction of dianemycin (magenta) with PfGST (red); **(D)** Interaction of carriomycin (green) with PfGST (red); **(E)** Interaction of etheromycin (pink) with PfGST (red); **(F)** Interaction of septamycin (white) with PfGST (red).

DISCUSSION

Polyether ionophore is a compound group used worldwide as an anticoccidial agent for animal husbandry (Novilla et al., 2017; Rutkowski and Brzezinski, 2013). Bacteria, especially soil-isolated *Streptomyces* sp., are known to be the main producers of polyether ionophore compounds. Several studies have stated that this compound is not only useful as an anticoccidial, but also as an antibacterial, antifungal, antiparasitic, antiviral, and has effects on cardiovascular, immunoregulatory, anti-inflammatory, herbicidal, and cytotoxic tumor cells (Kevin II et al., 2009; Rutkowski and Brzezinski, 2013). In addition, this compound is effectively capable of killing cancer stem cells and multidrug-resistant cancer cells (Rutkowski and Brzezinski, 2013). The general mechanism of action of the ionophore is to selectively complex with cations and facilitate the transport of these compounds across cell membranes (Novilla et al., 2017).

Table 3. Residue interaction between polyether ionophore and PfGST protein.

Ligand type	Compound name	Protein ligands interaction
Control ligands	Chloroquine	Hydrogen Bond: Gly14 Hydrophobic Interaction: Asn112, His107, Asn167, Leu18, Phe100, Gln104, Lys15, Tyr108, Asn111
Test ligands	Nigericin	Hydrogen Bond: **Gly14, <u>His107</u>** Hydrophobic Interaction: Leu115, Phe116, Asn114, **Asn111, Tyr108, Lys15, Gln104, Phe100, Asn167,** Tyr211, Tyr9, Val210
	Carriomycin	Hydrogen Bond: **Gly14** Hydrophobic Interaction: Tyr9, Phe116, Gln118, Un11, **Asn112**, Leu115, **Asn111**, **Tyr108, Gln104, His107, Asn167,** Tyr211, Gln73, **Phe100, Lys15,** Val59, Phe10
	Septamycin	Hydrogen Bond: **<u>Asn111,</u>** Tyr211 Hydrophobic Interaction: **His107, Gln104, Tyr108, Asn112,** Phe10, Tyr9, Val59, **Lys15, <u>Gly14</u>**
	Etheromycin	Hydrogen Bond: Tyr211, Tyr9 Hydrophobic Interaction: Pro60, Gln71, Ser72, Val59, **Lys15, Asn112, Tyr108, Asn111,** Ala41, Phe10, Phe42, Gln58
	Dianemycin	Hydrogen Bond: **<u>Asn111</u>**, Tyr211, **<u>Asn167</u>** Hydrophobic Interaction: Phe10, Tyr9, **Tyr108, Asn112, Gly14, His107, Lys15,** Leu115, **Gln104,** Phe116
	Lenoremycin	Hydrogen Bond: Phe42, Val59, Tyr9 Hydrophobic Interaction: Ala41, Asp40, Phe10, Tyr211, Leu115, **Asn111,** Gln58, Phe45

Bold letters indicate the similarity of interactions between the polyether ionophore compounds-PfGST complex when compared with chloroquine-PfGST.

<u>Underlined bold letters</u> indicate similar interactions, but different bonds between the polyether ionophore compounds-PfGST complex when compared to chloroquine-PfGST.

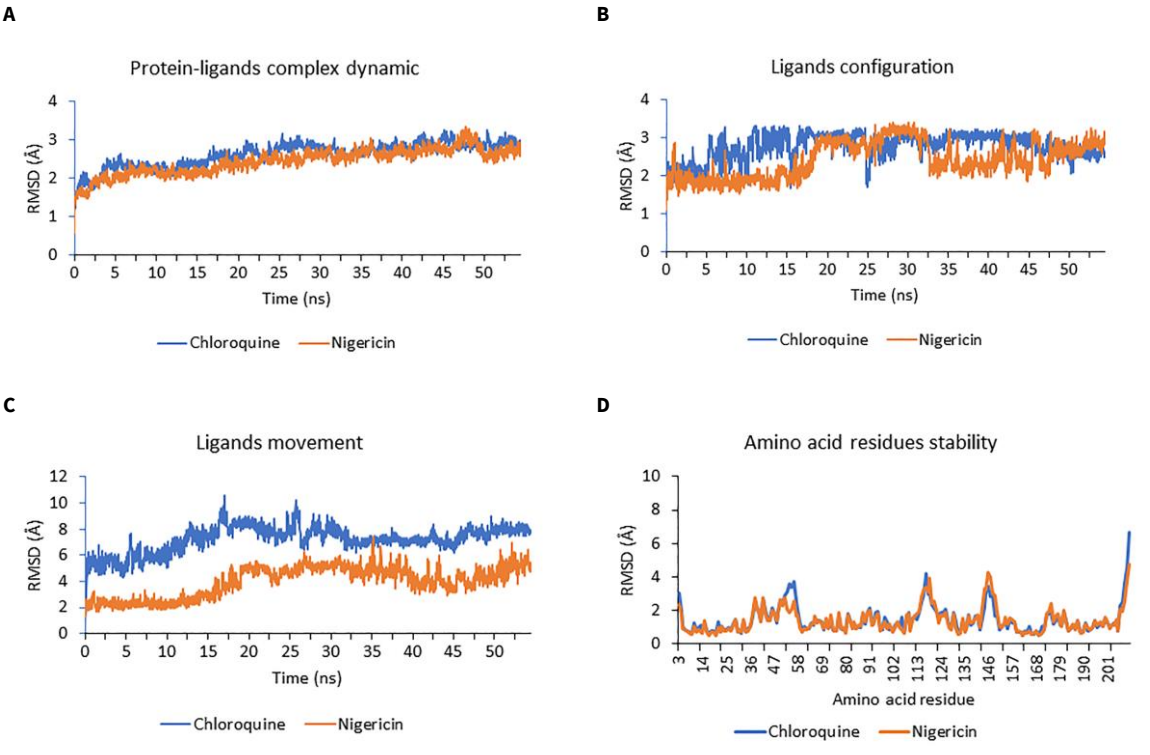


Figure 5. The molecular dynamic of PfGST-nigericin complex compared to PfGST-chloroquine complex.

(A) PfGST-nigericin complex shows lower compared to PfGST-chloroquine complex in RMSD protein-ligand complex; **(B)** The protein-ligand complex conformation; **(C)** The protein-ligand movement interaction analysis showed nigericin more stable than chloroquine; **(D)** The amino acid residue stability shows similarities between nigericin and chloroquine. RMSD: root mean square deviation.

There are several theories regarding the mechanism of action of polyether ionophores in inhibiting the development of *Plasmodium* parasites. A study stated that the polyether ionophore was similar to the antimalarial drug chloroquine (Adovelande and Schrével, 1996). Polyether ionophore is known to work by entering the intracellular organelle membranes and exchanging protons for cations. This will lead to alkalinization of the food vacuole and inhibition of lysosomal protein degradation. However, other mechanisms of the polyether ionophores have also been and are being investigated further (Adovelande and Schrével, 1996; Kevin II et al., 2009).

The polyether ionophore compounds that were successfully identified using LC-MS in this study were nigericin, lenoremycin, dianemycin, carriomycin, etheromycin, and septamycin. These compounds are part of the mobile carrier (true ionophores). The mobile carrier is a polycyclic polyether with an alkyl backbone, an oxygen-rich internal sac, and a terminal carboxyl group. Both of these things play an important role in the ability of the compound to bind to metal ions (Na et al., 2008). According to the Lipinski Rule of Five, these compounds do not meet the criteria for oral administration because of their large size and cannot be hydrogen acceptors, so other routes of administration, modifications, or other alternatives can be considered.

The target protein in this study was *Plasmodium falciparum* glutathione S-transferase (PfGST). PfGST protein is considered quite potential as a therapeutic target because the substrate-binding site to the protein is different from humans, especially at the active H-site (Hiller et al., 2006; Perbandt et al., 2015). In addition, PfGST activity was detected in all Plasmodium species and all intraerythrocytic phases (Hiller et al., 2006). This protein is also one of the targets of chloroquine. *In vitro*, chloroquine was able to inhibit PfGST at about 50% at a concentration of 70 M. Other compounds such as S-hexylglutathione, cibacron blue, and ferriprotoporphyrin IX (hemin) are also known to inhibit the action of PfGST (Harwaldt et al., 2002). However, the discovery of a substrate that can effectively inhibit this protein target is still being carried out. The active site of PfGST is located in the cleavage between the two domains of each monomer and consists of a G-site that binds to reduced glutathione and an H-site that can bind to a variety of substrates. H-site is very flexible and able to bind to large compounds, so other compounds have the potential to inhibit PfGST at this site. Through inhibition of PfGST, a substrate can interfere with the glutathione conjugation process, increase levels of cytotoxic peroxides, and increase the concentration of toxic ferriprotoporphyrin IX (FP) (Hiller et al., 2006).

The molecular docking results of these six polyether ionophores gave better binding affinities than chloroquine (Figs. 1 and 3). This indicates that these compounds have a stronger binding ability when interacting with the target protein. In line with this, several previous studies have shown that polyether ionophore has a potent ability as an antimalarial agent, both *in vitro* and *in vivo* (Adovelande and Schrével, 1996; Na et al., 2008; Otoguro et al., 2001; Rajendran et al., 2015). Of the six compounds, nigericin is one of the compounds that has been known to be higher and more selective as an antimalarial (Na et al., 2008). It was reported that nigericin's antimalarial activity at the nanomolar and picomolar scales is up to 30,000 times that of chloroquine. Nigericin is able to balance the entry of K and H ions across the lysosomal membrane and inhibit intralysosomal degradation (Adovelande and Schrével, 1996).

The best binding affinity among identified polyether ionophores was lenoremycin compound (-8.53 kcal/mol) with residue formed between the lenoremycin-PfGST complex and had similarity with chloroquine only hydrophobic interaction in Asn111. The dianemycin compound ranks second with a bond affinity of -8.30 kcal/mol. The same residues formed between the dianemycin-PfGST complex compared with chloroquine-PfGST were Tyr108, Asn112, His107, Lys15, and Gln105 as hydrophobic interactions. The Gly15 residue in the dianemycin-PfGST complex forms a hydrophobic interaction, while in the chloroquine-PfGST complex, it forms hydrogen bonds. Conversely, residues Asn167 and Asn111 in complex dianemycin-PfGST form hydrogen bonds, and hydrophobic interactions in complex form chloroquine-PfGST. Compounds nigericin is third with a binding affinity of -8.25 kcal/mol. The residues that are formed and are the same as chloroquine are hydrophobic interactions in Asn111, Tyr108, Lys15, Gln104, Phe100, and Asn167 and hydrogen bonds in Gly14. The His107 residue in the nigericin-PfGST complex forms hydrogen bonds, while in chloroquine, it forms hydrophobic interactions. Compounds carriomycin and septamycin have an equal binding affinity of -7.98 kcal/mol. Common residues between carriomycin-PfGST and chloroquine-PfGST are hydrophobic interactions at Asn112, Asn111, Tyr108, Gln104, His107, Asn167, Phe100, and Lys15 and hydrogen bond at Gly14. The septamycin-PfGST complex, compared with chloroquine, formed hydrophobic interactions in His107, Gln104, Tyr108, Asn112, and Lys15 and hydrogen bonds in Asn111. The Gly14 residue forms a hydrophobic interaction on the septamycin-PfGST complex and hydrogen bonds on chloroquine. The compound that ranks last is etheromycin, with a bond affinity of -7.7 kcal/mol. The residue formed and the same as chloroquine is a hydro-

phobic interaction on Lys15, Asn112, Tyr108, and Asn111.

The dynamic molecular study was carried out to analyze the interaction of protein-ligand polyether complexes selected from the docking study, which showed the best binding affinity results. In addition, in molecular dynamics, nigericin will be compared with chloroquine as a drug that has been used. Analysis of molecular dynamics was carried out by looking at the results of the RMSD measurement in Fig. 5. Based on the results of dynamic molecular data on the RMSD ligand-protein complex, two ligands showed very stable interactions with minimal fluctuations (Fig. 5A). The results of the conformational ligands also show the stability of the protein-ligand interaction bond which is indicated by the RMSD value. To support the results of the protein-ligand complex analysis, the MD analysis also shows the results of the RMSD Ligand movement. RMSD ligand movement is used to see how the protein-ligand complex interacts when moving. In the study, it was found that the nigericin-PfGST complex showed good stability of the protein-ligand complex interaction with RMSD values between 2.0-4.0 Å at least up to 30 ns with minimal fluctuation. Meanwhile, chloroquine showed interaction results with RMSD values of more than 6 Å at 50 ns. The PfGST-chloroquine complex interaction showed a high value of the RMSD ligand movement; this indicates the instability of the interaction when the movement occurs (Abkar et al., 2021).

CONCLUSION

Polyether ionophore has the potential ability as an antimalarial agent by assessing the binding affinity and bond formation interaction compared to the control. The data from bioinformatic analysis suggested that nigericin is the strongest candidate for an inhibitor of PfGST that may be beneficial for antimalaria. Nigericin has a higher binding affinity and can bind in the active site of PfGST compared to the control. Molecular dynamic simulation shows nigericin has a stability interaction complex from molecular dynamic analysis. Therefore, the examination activity of nigericin inhibition of PfGST still requires further research to confirm its effectiveness and toxicity against *Plasmodium* using *in vitro* or *in vivo* research methods.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Cahyono AW	Faratisha IFD	Erwan NE	Nugraha RYB	Putri AM	Fitri LE
Concepts or ideas	x					x
Design	x					x
Definition of intellectual content	x	x	x	x		x
Literature search	x	x	x		x	
Experimental studies	x	x				
Data acquisition	x	x	x			
Data analysis	x	x		x		
Statistical analysis	x	x		x	x	x
Manuscript preparation	x	x	x	x	x	x
Manuscript editing	x	x	x	x	x	x
Manuscript review	x	x	x	x	x	x

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