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Molecular docking study of *Zingiber officinale* Roscoe compounds as a mumps virus nucleoprotein inhibitor

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ABSTRACT

Background: *Mumps virus (MuV) can trigger severe infections, such as parotitis, epididymo-orchitis, and meningitis. The effectiveness of MuV vaccine administration has been proven, but current outbreaks warrant the development of antivirals against MuV. Zingiber officinale var. Roscoe or ginger is often used as an alternative remedy. Currently, there are no known in vitro or in vivo studies that investigate ginger as an MuV antiviral.* ***Purpose:*** *This study aims to evaluate the antiviral potency of the bioactive compounds in Zingiber officinale var. Roscoe against MuV.* ***Methods:*** *Antiviral activity screening was conducted by druglikeness analysis, antiviral probability, molecular docking, and molecular dynamic simulation.* ***Results:*** *As an antiviral, 6-shogaol from Zingiber officinale var. Roscoe has potency against MuV. It has a good binding affinity and can establish interactions with the binding domain of the target protein by forming hydrogen, Van der Waals, and alkyl bonds.* ***Conclusion:*** *The complex of 6-shogaol_NP was predicted to be volatile but stable for triggering inhibitory activity. However, these results must be proved by in vivo and in vitro approaches to strengthen the scientific evidence.*

Keywords: *communicable disease; medicine; mumps; nucleoprotein; Zingiber officinale*
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INTRODUCTION

Mumps virus (MuV) belongs to the Paramyxoviridae family. This virus causes acute generalized viral infection that is often prominently manifested as parotitis, a nonsuppurative swelling and tenderness of the salivary (parotid) glands, with unilateral or bilateral involvement of the glands. Meningitis and epidydymo-orchitis represent the two most important extra-salivary manifestations of this infection.[1] The administration of MuV vaccine in children has been proven highly effective in suppressing the incidence of mumps. However, recent global outbreaks that especially affect the adult population warrant the discovery of an antiviral against MuV.[1] MuV became an outbreak in America in June 2017 and in Japan in July 2015 and affected 25,000 people.[2,3] In the past, this virus was introduced by Hippocrates (circa fifth century BC) and was referred to in his first book, *Book of Epidemics*. However, the mechanism of MuV infection was only discovered in 1930 through experimental animal studies by Johnson and Goodpasture with Koch's postulate approach.[4,5]

MuV contains replication enzymes, such as RNA-dependent RNA polymerase (vRdRp) with large protein (L), nucleocapsid protein (NP) or genome virus sheath, and phosphoprotein (P). These proteins have important roles as transcription and replication machines in MuV.[6]

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The template that initiates the replication and synthesis of MuV comes from the RNA genome virus (vRNA). Subsequently, vRNA can establish a complex with NP that generates helix-shaped proteins or ribonucleoproteins (RNPs) to avoid degradation.[7] RNP can associate with P and L proteins to make vRdRp. The role of the L protein in this complex is to trigger the RNA synthesis process, which consists of initiation, elongation, and termination.[8] The NP protein in MuV plays a role in the formation of the vRNA complex to avoid degradation and initiate the replication process. Inhibition of the NP protein's activity will disturb the initiation of the replication process by increasing the degradation of vRNA in MuV.

Zingiber officinale var. Roscoe or ginger is often used as an alternative medication for inflammation and diabetes and is also used as an antibacterial and antioxidant.[9] Some chromatography research studies show that *Zingiber officinale* var. Roscoe contains the bioactive compounds 6-shogaol, 12-gingediol, 4-gingerol, gingerdione, 6-gingediol, 8-gingerol, methyl-6-shogaol, zingerone, 10-gingerol, methyl-6-gingerol, and 6-gingerol.[10] In vitro research shows that *Zingiber officinale* var. Roscoe has potency as an antiviral on Vero cell-lines infected with Chikungunya virus. The research shows that there is an increase in the viability of cells of about 51.0%.[11] In vitro and in vivo research show that gingerone/gingerol can affect the replication of influenza-A virus by inhibiting the overexpression of type 1 and type 2 of the Janus Kinase protein. Previous research has not used *Zingiber officinale* var. Roscoe to combat mumps infections. Likewise, antiviral drugs derived from natural ingredients for mumps have not yet been discovered. Hence, this research is essential to reveal the potency of the bioactive compounds in *Zingiber officinale* var. Roscoe that inhibit MuV replication.

MATERIALS AND METHODS

Bioactive compounds from *Zingiber officinale* var. Roscoe that were used in this research consisted of 6-shogaol, 12-gingediol, 4-gingerol, gingerdione, 6-gingerdiol, 8-gingerol, methyl-6-shogaol, zingerone, 10-gingerol, methyl-6-gingerol, and 6-gingerol.[10] The three-dimensional (3D) structure in .sdf file format, collision-induced dissociation (CID), formula, and the *Canonical simplified molecular-input line-entry system* (SMILE) of each compound were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/). The 3D structures in .pdb format were retrieved under "ligand minimization" from OpenBabel v2.3.1. At the same time, the target protein in MuV, which is an NP (7EWQ), was retrieved from RCSB PDB (https://www.rcsb.org/) (Figure 1).

The Canonical SMILE from the bioactive compounds 6-shogaol, 12-gingediol, 4-gingerol, gingerdione, 6-gingediol, 8-gingerol, methyl-6-shogaol, zingerone, 10-gingerol, methyl-6-gingerol, and 6-gingerol were used for druglikeness analysis with the SwissADME web server (http://www.swissadme.ch/). Lipinski's "rule of five" plus the rules of Ghose, Veber, Egan, and Muege and a bioavailability score must be fulfilled by the compounds in order for them to be categorized as a drug-like molecule. This prediction aimed to determine the resemblance and the ability of the chemical compounds query with the drug that refers to the rules of druglikeness and shows general activity.[12]

Bioactive compounds from *Zingiber officinale* var. Roscoe that were categorized as a drug-like molecule were identified as a likely antiviral with the PASS web server (http://way2drug.com/PassOnline/). Query compounds are considered to have a positive prediction if the probability

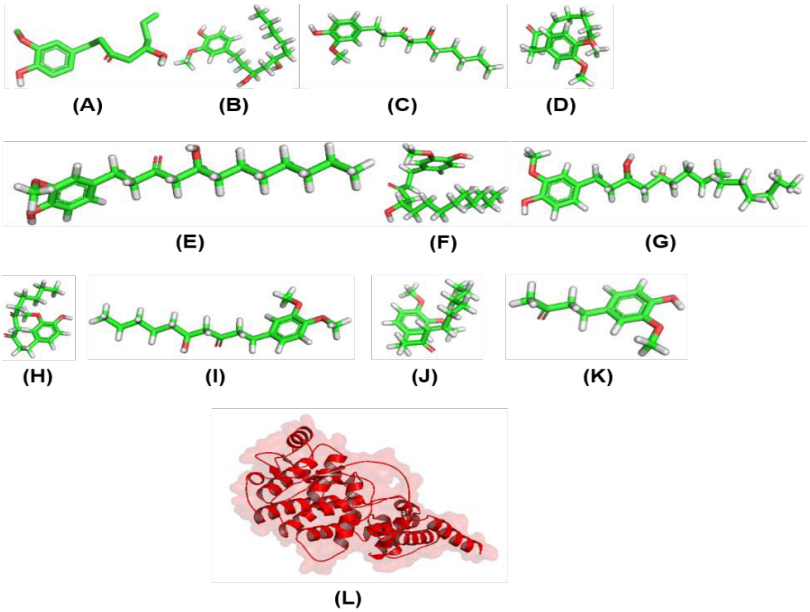

Figure 1. Molecular docking visualization: (A) 6-shogaol (B) 12-gingediol (C) 4-gingerol (D) gingerdione (E) 6-gingediol (F) 8-gingerol (G) methyl-6-shogaol (H) zingerone (I) 10-gingerol (J) methyl-6-gingerol (K) 6-gingerol (L) MuV NP.

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activation value (Pa) is greater than 0.3, denoting that they are a good candidate for being an antiviral agent.[13]

Molecular docking simulation between the bioactive compounds from *Zingiber officinale* var. Roscoe with MuV NP were conducted by PyRx v0.9.9 (Scripps Research, USA) with an academic license. The docking aims to determine the ligand activity with the target protein, referring to the binding affinity value (kcal/mol). The ligand with the most negative binding affinity is predicted to trigger specific biological activity on the target protein.[14,15] Three-dimensional visualization of the molecules from the docking results was conducted by PyMol v2.5.2 (Schrodinger Inc., USA) with an academic license.[16,17]

The molecule complexes from the docking results with the most negative binding-affinity value were then identified by using Discovery Studio Visualizer™ v16.1 (Dassault Systèmes SE, France) for the chemical interactions and bonds. The types of chemical bonds that can be identified from the docking results are hydrogen, hydrophobic, alkyl, electrostatic, and Van der Waals.[18]

The molecular dynamic simulation in the molecule complex with the most negative binding-affinity value was conducted by the CABS-Flex v2.0 web server (http://biocomp.chem.uw.edu.pl/CABSflex2). The molecular dynamic analysis aimed to identify the interaction stability in the molecule complex by assigning a root-mean-square-fluctuation (RMSF) value. This interaction is considered stable if the molecule has an RMSF value below 3 Å.[19]

RESULTS

Druglikeness acts as an important factor to identify the query compounds' activity resemblance to drug molecules. The druglikeness prediction refers to rules proposed by Lipinski, Ghose, Veber, Egan, and Muege and also a bioavailability score. In effect, the rules explain some physicochemistry that has to be satisfied by the query compounds, such as hydrogen-donor bonds, acceptor, molar refractivity, partition coefficient (Log P), molecular weight, topological polar surface area (TPSA), atomic number, and rotatable bonds.[20] The query compounds should have a minimum bioavailability value of 0.55 to be categorized as a drug-like molecule. Compounds with that value will easily be absorbed by the body because of their good pharmacokinetics value.[21] The results from this research show that all the bioactive compounds from *Zingiber officinale* var. Roscoe are considered collectively as a drug-like molecule because the compounds fit the druglikeness parameters (Table 1).

The activity prediction as an antiviral was conducted from the bioactive compounds that were considered as a drug-like molecule. The antiviral activity was predicted by the probability activation (Pa) having a value above 0.3 (medium confidence) and probability inhibition (Pi) that was not greater than Pa. However, the prediction was general and was only a theoretical result and should be proved by further experimentation.[13,22] This research shows

Table 1. Druglikeness prediction results

Compounds	Druglikeness Parameters					
	Lipinski	Ghose	Veber	Egan	Muege	Bioavailability Score
6-shogaol	Yes	Yes	Yes	Yes	Yes	0.55
12-gingediol	Yes	Yes	No	Yes	No	0.55
4-gingerol	Yes	Yes	Yes	Yes	Yes	0.55
gingerdione	Yes	Yes	Yes	Yes	Yes	0.55
6-gingediol	Yes	Yes	Yes	Yes	Yes	0.55
8-gingerol	Yes	Yes	No	Yes	Yes	0.55
methyl-6-shogaol	Yes	Yes	Yes	Yes	Yes	0.55
zingerone	Yes	Yes	Yes	Yes	No	0.55
10-gingerol	Yes	Yes	No	Yes	No	0.55
methyl-6-gingerol	Yes	Yes	No	Yes	Yes	0.55
6-gingerol	Yes	Yes	Yes	Yes	Yes	0.55

Table 2. Antiviral probability score

Compounds	CID	Formula	Antiviral Probability		Prediction Result
			Pa	Pi	
6-shogaol	5281794	$C_{17}H_{24}O_3$	0.477	0.034	Positive
12-gingediol	86196540	$C_{23}H_{40}O_4$	0.644	0.004	Positive
4-gingerol	5317596	$C_{15}H_{22}O_4$	0.543	0.013	Positive
gingerdione	162952	$C_{17}H_{24}O_4$	0.402	0.089	Positive
6-gingediol	101660275	$C_{17}H_{28}O_4$	0.644	0.004	Positive
8-gingerol	168114	$C_{19}H_{30}O_4$	0.553	0.012	Positive
methyl-6-shogaol	91721066	$C_{18}H_{26}O_3$	0.498	0.025	Positive
zingerone	31211	$C_{11}H_{14}O_3$	0.384	0.052	Positive
10-gingerol	168115	$C_{21}H_{34}O_4$	0.553	0.012	Positive
methyl-6-gingerol	70697235	$C_{18}H_{28}O_4$	0.574	0.009	Positive
6-gingerol	442793	$C_{17}H_{26}O_4$	0.553	0.012	Positive

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Table 3. Binding affinity from molecular docking simulation

Compounds	CID	Molecular Weight (g/mol)	Target	Binding Affinity (kcal/mol)
6-shogaol	5281794	276.4	MuV NP	-6.5
12-gingediol	86196540	380.6	MuV NP	-6.3
4-gingerol	5317596	266.33	MuV NP	-6.1
gingerdione	162952	292.4	MuV NP	-6.0
6-gingediol	101660275	296.4	MuV NP	-5.8
8-gingerol	168114	322.4	MuV NP	-5.8
methyl-6-shogaol	91721066	290.4	MuV NP	-5.6
zingerone	31211	194.23	MuV NP	-5.5
10-gingerol	168115	350.5	MuV NP	-5.3
methyl-6-gingerol	70697235	308.4	MuV NP	-5.3
6-gingerol	442793	294.4	MuV NP	-4.9

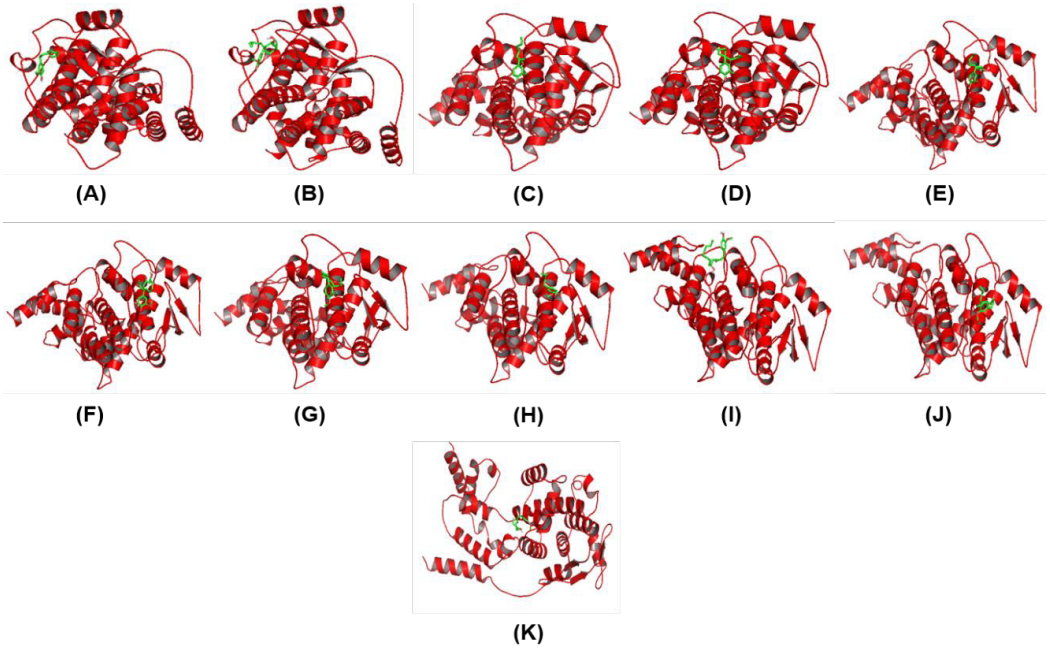

Figure 2. Molecular docking visualization: (A) 6-shogaol_NP (B) 12-gingediol_NP (C) 4-gingerol_NP (D) gingerdione_NP (E) 6-gingediol_NP (F) 8-gingerol_NP (G) methyl-6-shogaol_NP (H) zingerone_NP (I) 10-gingerol_NP (J) methyl-6-gingerol_NP (K) 6-gingerol_NP.

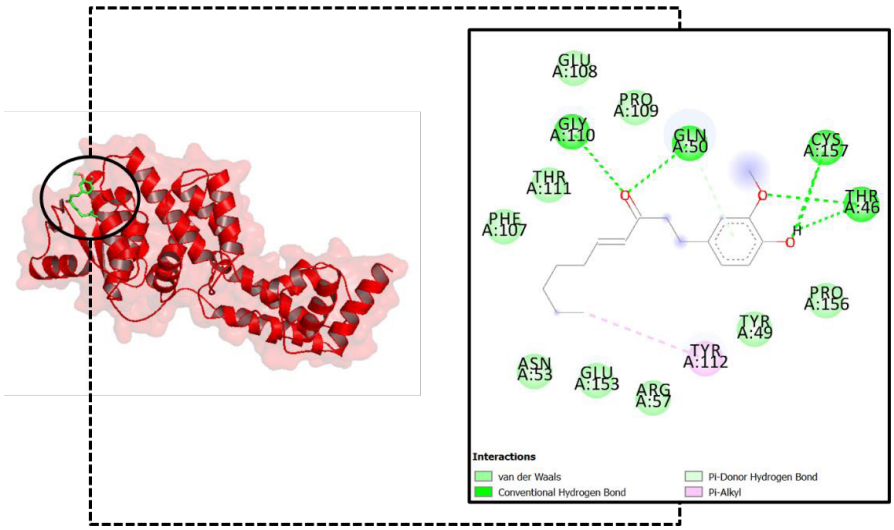

Figure 3. Structural visualization and ligand–protein interactions of 6-shogaol_NP—the three-dimensional structure was displayed by PyMol v2.5.2 (Schrödinger Inc., USA) with an academic license and Visualizer™ v16.1 for molecular interaction

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that all bioactive compounds from *Zingiber officinale* var. Roscoe have positive prediction as an antiviral with a Pa value above 0.3 (Table 2).

Molecular docking aims to predict the binding activity of the ligand with the target protein, pattern of interaction at the domain protein, and ligand activity.[17] The determination of the inhibition activity of a ligand on the target protein can be predicted from the molecular docking method. Grids from the docking method are used to direct the ligand to the specific domain on the target protein, especially on the aimed domain.[23] This research used the bioactive compounds from *Zingiber officinale* var. Roscoe as the ligand and MuV NP as the target protein. The autogrid positions for the molecular docking simulation were center (Å) X: 132.028 Y: 224.440 Z: 160.519 and dimensions (Å) X: 76.725 Y: 48.911 Z: 71.149 with the grid covering the entire target-protein domain. The molecular-docking result shows that 6-shogaol had a binding affinity value that was more negative than the other compounds, that is, 6.5 kcal/mol at MuV NP (Table 3). Hence, 6-shogaol is predicted to have stronger bonds than the other compounds and therefore trigger inhibitory activity at MuV NP. The 3D visualization of the molecular-docking result is shown as the transparent surface structure, corkscrew-like objects, lines, and color selection (Figure 2).

The molecular-docking result of 6-shogaol_NP complex was then analyzed based on the position and types of the chemical bonds that were formed on that complex. A weak molecular interaction is formed when the ligand molecule interacts with the specific domain of the target protein.[24] The interaction consists of Van der Waals, hydrogen, alkyl, hydrophobic, and electrostatic effects that act to trigger the biological response of some proteins. The hydrogen, hydrophobic, Van der Waals, and alkyl bonds that are formed in drug molecules lead to increased stability and bond strength.[18] When 6-shogaol interacts with the MuV NP's domain, 6-shogaol can form hydrogen, Van der Waals, and alkyl interactions (Figure 3).

The chemical interaction stability that was formed on the 6-shogaol-NP complex in this research can be predicted with molecular dynamic (MD) simulation. MD analysis aims to identify the interaction stability in the molecule complex with reference to the root-mean-square-fluctuation value (RMSF). The chemical interaction in this molecule complex that is formed can be considered stable because the interactions should have an RMSF value below 3 Å. The RMSF value of the 6-shogaol binding domain in MuV NP consisted of Phe107 (0.434 Å), Thr111 (1.546 Å), Glu108 (0.722 Å), Pro109 (1.385 Å), Pro156 (2.354 Å), Tyr49 (0.219 Å), Arg57 (0.227 Å), Glu153 (1.320 Å), Asn53 (0.254 Å), Gly110 (1.830 Å), Gln50 (0.295 Å), Cys157 (2.671 Å), Thr46 (0.541 Å), and Tyr112 (0.898 Å) according to the CABS-Flex 2.0 server (http://biocomp.chem.uw.edu.pl/CABSflex2/job/20ed7c1748559f0/). The molecule complex of 6-shogaol_NP is considered stable because it has an RMSF value below 3 Å (Figure 4).

DISCUSSION

MuV belongs to the Paramyxoviridae family. This virus causes an acute generalized viral infection that is often prominently manifested as parotitis, a nonsuppurative swelling and tenderness of salivary (parotid) glands,

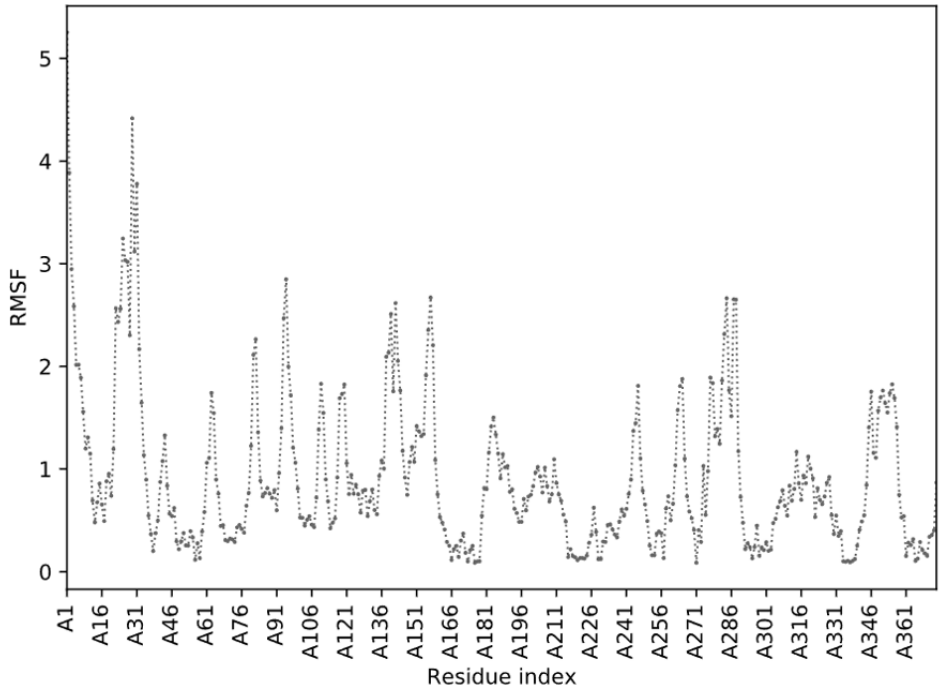

Figure 4. Molecular dynamic simulation results—the values of RMSF have fluctuations and are plotted against the 6-shogaol_NP complex-residue index

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with unilateral or bilateral involvement of the glands. Meningitis and epidydymo-orchitis represent the two most important extra-salivary manifestations of this infection.[1] MuV has replication enzymes, such as RNA-dependent RNA polymerase (vRdRp) with large protein (L), NP or genome virus sheath, and phosphoprotein (P). These proteins have important roles as transcription and replication machines in MuV.[6] NP protein in MuV plays a role in the formation of the vRNA complex to avoid degradation and initiate the replication process. Inhibition of the NP protein's activity will disturb the initiation of the replication process through an increase of degradation of vRNA in MuV.

Druglikeness prediction refers to rules used by Lipinski, Ghose, Veber, Egan, and Muege as well as a bioavailability score. Essentially, the rules explain some physicochemistry that has to be fulfilled by the query compounds, such as hydrogen donor bonds, acceptor, molar refractivity, partition coefficient (Log P), molecular weight, topological polar surface area (TPSA), atomic number, and rotatable bonds.[20] The results from this research showed that all the bioactive compounds from *Zingiber officinale* var. Roscoe could collectively be considered a drug-like molecule.

Molecular docking aims to predict the binding activity of the ligand with the target protein, the pattern of interaction at the domain protein, and ligand activity.[17] This research used bioactive compounds from *Zingiber officinale* var. Roscoe as the ligand and MuV NP as the target protein. The molecular-docking results show that 6-shogaol is predicted to have stronger bonds than the other compounds and could trigger inhibitory activity at MuV NP. A weak molecular interaction is formed when the ligand molecule interacts with the specific domain of the target protein.[24] When 6-shogaol interacts with the MuV NP's domain, 6-shogaol can form hydrogen, Van der Waals, and alkyl interactions. The chemical interactions in this molecule complex can be considered stable if they have an RMSF value below 3 Å.[19] Because it has an RMSF value below 3 Å, 6-shogaol-NP is considered stable.

The compound from *Zingiber officinale* var. Roscoe, 6-shogaol, has potency as an antiviral for MuV because it has a binding affinity that is more negative than the others and can form hydrogen, Van der Waals, and alkyl bonds in the target protein's binding domain. The complex of 6-shogaol_NP fluctuates but is stable and can trigger inhibitory activity at the target. However, this research must be proved and further explored by in vivo and in vitro approaches to strengthen the scientific evidence.

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