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In silico study of the essential oil compounds of ginger and thyme on Coronavirus-2 receptors

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ABSTRACT

Coronavirus-2 (SARS-Cov-2) is a virus that attacks the respiratory system and causes the Covid-19 pandemic. After the pandemic, prevention and appropriate therapy research continue to be carried out to anticipate the emergence of more dangerous viruses. In line with the culture of consuming herbs that has arisen due to the effects of the pandemic, in this study, an insilico screening was carried out for essential oil compounds produced by ginger and thyme herbs which have been widely consumed by the public. The aim of the research was to find the essential oil content that has the most potential as an antiviral against coronavirus-2. The research method was carried out in silico, including ligand preparation, receptor and method validation, and analysis of ligand-receptor binding interactions using the AutoDoc 4.2.6 program. As a comparison, a study was conducted on remdesivir and favipiravir, which have been used as antivirals. The three components that have the most potential based on the calculation of the free energy value, were determined by the ADMET parameters using the Admet lab 2.0 program. The results showed that the three components in the essential oil exhibited better interactions when compared to remdesivir and favipiravir at the 3-Cl protease and spike glycoprotein receptors. The results of the insilico study and ADMET prediction test showed that of the three most potent compounds, α -farnesen was the most potent and safe to use

Keywords: *in silico*, ginger and thyme herbs, 3-Cl protease, spike glycoprotein coronavirus-2

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52 INTRODUCTION

53 The COVID-19 pandemic, which was developing rapidly due to coronavirus-2, required an
54 effective therapeutic strategy so that it could easily go through clinical trials to reduce human, social,
55 and economic impacts. The reuse of previously approved drugs such as remdesivir and favipiravir
56 allowed antiviral drugs to be used safely immediately (Grein et al., 2020). However, studies on some
57 of these drugs were incomplete because they only approached classic viral targets (Singh et al., 2020).
58 In addition, most of the drugs that have been approved were not clinically proven to be effective
59 against coronavirus-2 because they showed marginal effectiveness and conflicted clinical trials
60 (Bellera et al., 2021). In some cases, many people did not receive the vaccine. On the other hand, some
61 virus variants may be resistant to the vaccines that have been used. Therefore, it was still necessary to
62 develop new compounds that were effective against coronavirus-2.

63 Essential oils have long been developed and used as antivirals (Ma & Yao, 2020). Due to their
64 lipophilic property, essential oils could easily penetrate viral cell membranes and cause membrane
65 disruption, then synergistically affect replication and produce effects on the host, namely
66 bronchodilation and mucus secretion (Asif et al., 2020). da Silva et al., 2020 conducted a molecular
67 docking study of 171 essential oil compounds of various herba plants against various types of
68 receptors. It had been known that thyme (*Thymus vulgaris*) and ginger (*Zingiber officinale*) were
69 estimated to have the potential to produce essential oils that act synergistically with anti-virals,
70 improved anti-viral performance and relieved some of the symptoms that appear. However, da Silva
71 et al., 2020 had not described the interactions of these compounds against protease-derived receptors
72 such as 3-Chromotrypsin like protease (3-Cl protease) and spike glycoprotein transmembrane
73 receptors. On the other hand, da Silva et al. (2020) did not analyze the results by comparing the anti-
74 viral drugs used. Therefore, in this research, an insilico study was carried out on essential oil
75 components in thyme and ginger using the AutoDoc 4.2.6 program and observations of anti-viral
76 drugs, namely favipiravir and remdesivir on 3-Cl protease receptors and spike glycoproteins. We
77 examined the three components that had the best interactions; their adsorption, distribution,
78 metabolism, excretion, and toxicity properties would be examined. It was expected that the results of
79 this research could explain the effectiveness of the essential oils contained in thyme and ginger herbs
80 when compared to the anti-virals that have been used previously, as well as explain the
81 pharmacokinetic properties and toxicity of related compounds.

83 MATERIALS AND METHOD

84 Materials

85 In this experiment, the tools consist of hardware and software. The hardware tools were a set of
86 laptop with Windows 10, 3.10 GHz, 4.00 GB RAM, 64-bit operating system, and x64-based processor.
87 The software tools were Autodock 4.2.6 (Autodock Tools 1.5.6), Discovery Studio Visualizer 19.1.0,
88 VMD 1.9.3, Admet lab 2.0, and internet connection. 3.2.2.

89 The materials used in this study were the structure of the ginger components, namely α -zingiberin,
90 β -sesquifelandren, ar-curcumin, α -felandren and α -farnesen and the thyme components, namely
91 thymol, carvacrol, ρ -simene, β -karyofilen and γ -terpinen. All the structure were downloaded from
92 the Pubchem website (<https://pubchem.ncbi.nlm.nih.gov/>). The receptor material used was a three-
93 dimensional structure of 6M2N (3-Cl protease in complex with an inhibitor) and 6VXX (SARS-CoV-2
94 spike glycoprotein (closed)), which were downloaded from the Protein Data Bank (www.rscb.org)
95 (Myler et al., 2009; Zhao et al., 2022). The antiviral drugs used were Remdesivir and Favipiravir,
96 which were downloaded from the Pubchem website (<https://pubchem.ncbi.nlm.nih.gov/>).

98 Methods

99 The major components (>4%) of essential oils components that have been screened, according to
100 da Silva et al. (2020), were selected. The chemical structure of α -zingiberin, β -sesquifelandren, ar-
101 curcumin, α -felandren, α -farnesen thymol, carvacrol, ρ -simene, β -karyofilen, γ -terpinen, favipiravir,

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102 and remdesivir was obtained from the PubChem database. The collected Structure Data File (SDF)
103 files of these compounds were converted into PDB format using Online SMILES Translator. All the
104 ligands were optimized, and the lowest energy was determined.

105 The receptor target from the Protein Data Bank, 3 Cl-protease (PDB:6M2N) and spike glycoprotein
106 (PDB:6VXX), were used in the molecular docking. Receptor was prepared by using Autodock 4.2.6.
107 programs (Forli et al., 2016). The active sites of ligand and protein were analyzed using Biovia
108 Discovery Studio.

109 The validation of the molecular docking method was carried out by redocking the receptor and its
110 native ligand and then determining the size and position of the grid box for the docking process. The
111 receptor was separated from its native ligand and re-docked with its native ligand. The process was
112 called valid if the value of RMSD was less than 2 Å.
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114 Data Analysis

115 The docking process was carried out using the AutoDock 4.2.6 program, while Discovery Studio
116 Visualizer 19.1.0 was used to obtain interaction. The results of docking the receptors with potential
117 ligands (essential oils from thyme and ginger) were observed from the free energy value (ΔG) to
118 determine the potential ligands that have interactions with the receptors. The interaction between the
119 receptor and the potential ligand was compared to antiviral ligand. The physicochemical properties,
120 ADMET, and toxicity studies were carried out on the three most potent substances and reference
121 compounds. The results obtained were then compared and analyzed further with Admet lab 2.0. (Dong
122 et al., 2018).
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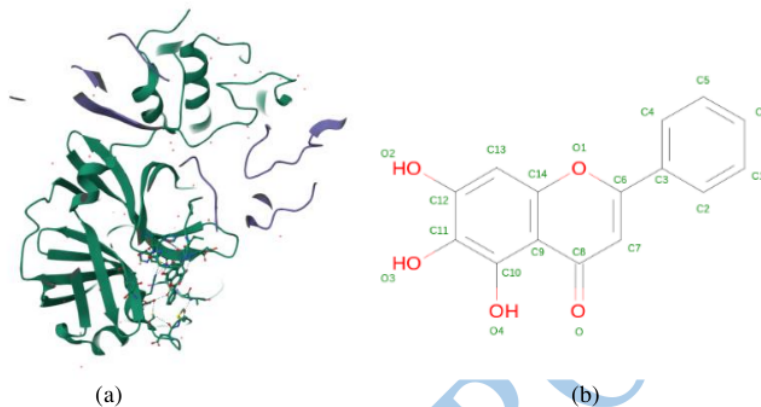
124 RESULT AND DISCUSSION

125 In this study, we used the compounds from ginger and thyme herbs. The selection of these two
126 plants was based on the availability of herbs in Indonesia and their effectiveness as anti-viral drugs,
127 which were tested in vitro on RC-37 cells using the plaque reduction method with IC 50 levels for
128 ginger was 1 $\mu\text{g/mL}$, and for thyme was 7 $\mu\text{g/mL}$. The ligands used in this study were the structure of
129 the ginger components, namely α -zingiberin (32.1%), β -sesquifelandren (10.9%), α -curcumin
130 (15.2%), α -felandren (4.4%), γ -campholenol (1.4%), and α -farnesene (7.2%) and the thyme component, namely thymol
131 (43.9%), carvacrol (14.4%), p -cymene (10.5%), β -karyofilen (7%) and γ -terpinene (5.1%) (da Silva
132 et al., 2020).

133 The 3-Cl protease (PDB: 6M2N) receptor was a 3C-like proteinase construction composed of an A
134 chain with 306 sequences (Figure 1.a.) and one native ligand 5,6,7-trihydroxy-2-phenyl-4H-chromen-
135 4-one (C15H10O5) (Figure 1.b.) (Su et al., 2020). The receptor has a total weight of 136.38 kDa with
136 a total number of atoms: 9544. The selection of the 3 chromotropin like-protease receptor was based
137 on potential antiviral therapeutic targets that were currently being developed because these proteases
138 were required for viral transcription and replication. The specificity of 3Cl-protease media was
139 conserved compared to different coronaviruses and was similar to the main picornavirus protease,
140 making it an ideal target for the development of broad-spectrum antiviral drugs (Pillaiyar et al., 2016).
141 The 5 replicates receptor validation results showed a RMSD value of 1.98 ± 0.0037 Å, which was less
142 than 2 Å, so the method was valid. Conservation residue was found in the 3-Cl protease binding
143 pocket and, in this study, was the main target for its antiviral activity.

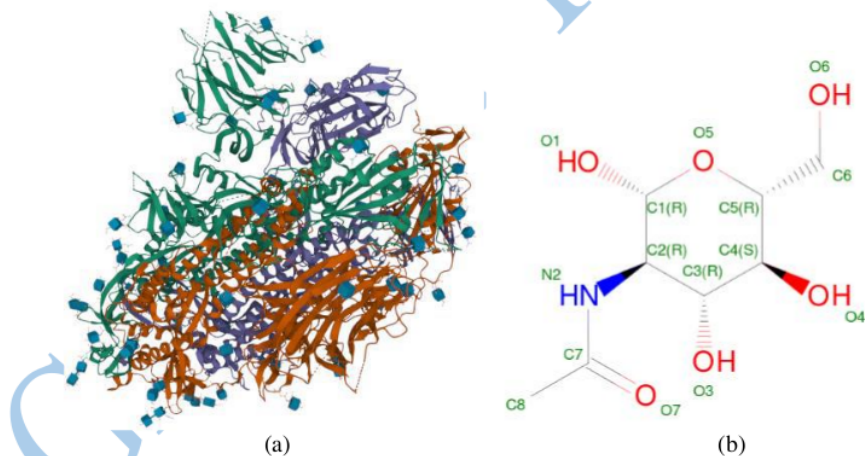
144 The spike glycoprotein receptor has a total weight of 438.26 kDa with a total atomic count of
145 23694, classified as a spike glycoprotein of severe acute respiratory syndrome coronavirus 2 virus
146 expressed in humans. The receptor consists of chain of two protein entities with chains A, B, and C
147 attached to 2-acetamido-2-deoxy-beta-D-glucopyranose-(1-4)-2-acetamido-2-deoxy-beta-D-
148 glucopyranose and the D,E,F,G,H,I, J,K,L,M,N,O,P,Q and r chains attached to 2-acetamido-2-deoxy-
149 beta-D-glucopyranose (Figure 2.a.). The ligand assigned was 2-acetamido-2-deoxy-beta-D-
150 glucopyranose (C₈H₁₅NO₆) (Figure 2.b.) (Myler et al., 2009). The selection of the spike glycoprotein
151 receptor was based on its uniqueness in mediating coronavirus entry into cells through interaction with

152 Angiotensin Converting Enzyme-2. Because of its location on the surface, it could be developed to
 153 become the main target for drug development and vaccine design (Myler et al., 2009). The 5 replicates
 154 validation showed a RMSD value of $1.88 \pm 0.0044 \text{ \AA}$, which was less than 2 \AA , so the method could be
 155 declared valid.



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Figure 1.(a) 3-Cl protease with inhibitor in 3D and (b) ligand 5,6,7-trihydroxy-2-phenil-4H-chromen-4-on ($C_{15}H_{10}O_5$)



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Figure 2. (A) spike glycoprotein complex and (B) ligand 2-acetamido-2-deoxy-beta-D-glucopyranose ($C_8H_{15}NO_6$)

The results of docking the compounds with the two receptors were carried out 3 times and expressed in the mean free energy value (ΔG), which is shown in Table 1.

173 **Table 1. The docking compounds in ginger and thyme against Coronavirus receptors**

Compound	Interaction with the 3-Cl protease		Interaction to the spike glycoprotein	
	ΔG (kcal/mol)	protein residue	ΔG (kcal/mol)	protein residue
α -zingiberin	-6,10	HIS41,MET49	-7,60	LEU226
α -farnesen	-7,24	HIS41,MET49,CYS44	-8,70	ILE119,VAL227,TYR170, LEU229,PHE168,ILE128
β -sesquifelandren	-6,90	HIS41,MET49,CYS44, MET165,PRO52	-8,34	ILE119,TYR170,ILE203, PHE192, TRP104
Ar-curcumin	-7,10	HIS41,MET 49,CYS44	-8,28	ILE119,VAL126, TYR170
α -felandren	-4,70	HIS41,CYS44, MET165,PRO52	-5,50	ILE119,VAL126,ILE103, VAL227,PHE192,TRP104
Timol	-4,60	HIS41,MET165	-5,50	VAL126,SER205
carvacrol	-4,70	HIS41,MET165	-5,50	VAL126,PHE192
p-simene	-4,80	HIS41,MET49	-5,40	VAL126,PHE192
β -caryofilen	-5,60	HIS41,	-5,90	VAL126
γ -terpinen	-4,70	HIS41,MET49,CYS44, MET165,PRO52	-5,40	VAL126,HIS207

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173 **Table 2. The docking compounds in favipiravir and remdesivir against Coronavirus receptors**

Compound	Interaction with the 3-Cl protease		Interaction to the spike glycoprotein	
	ΔG (kcal/mol)	protein residue	ΔG (kcal/mol)	protein residue
Favipiravir	-5,10	HIS41,MET49,CYS44, HIS164,ARG188,ASP187, PRO52,ASP48	-4,64	ILE119,PRO225,GLN134, ASN137,LEU110,GLN239
Remdesivir	-6,24	HIS41,MET49,CYS44, ASN142,ASP187,GLU166, ARG188,THR190	-6,22	PRO225,LYS41, PHE43, GLY283, ASP40

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177 The important role of 3-Cl protease in converting lipoproteins into functional proteins in viral
 178 replication made the receptor an attractive target for the development of compound inhibitors. The
 179 interactions that occur between the 10 compounds and the antiviral drugs with the receptor (Tables 1
 180 and 2) show π - π interactions between compounds with the amino acid HIS41 and π -alkyl interactions
 181 with amino acids MET 4. In some compounds that have small ΔG values, namely α -farnesen (-7.24),
 182 β -sesquifelandren (-6.90), and Ar-curcumin (-6.10) as well as favipiravir (-5.10) and remdesivir (-
 183 6.24), the van der waals interaction with CYS44 also occurred. However, this did not appear in γ -
 184 terpinen (-4.70), which also has interactions with CYS44 but has a large ΔG . It was suspected that this
 185 was due to the large space barrier effect on γ -terpinen. The results of this study were broadly in line
 186 with the research conducted by (Benhander & Abdusalam, 2022), who conducted an insulin Allium
 187 roseum study on the 3-Cl protease (6M2N) receptor.

188 The glycoprotein spike receptor interacts with ACE-2 in mediating the coronavirus to enter cells.
 189 The interactions that occurred between the 10 herbs compounds (Table 1) showed hydrophobic
 190 interactions between the compounds with the amino acid ILE119, and the three compounds with small
 191 ΔG also had hydrophobic interactions with TYR170. The results of this analysis are in line with
 192 research conducted by (Rolta et al., 2021). In the comparison compound favipiravir there was a

193 hydrophobic interaction with the amino acid ILE119 and a pi-sigma interaction with the amino acid
194 PRO225 while in remdesivir there was an interaction of pi-sigma with the amino acid PRO225 and a
195 π - π interaction with PHE43. The results of research on favipiravir and remdesivir were in line with
196 research conducted by (Veerasamy & Karunakaran, 2022).

197 Favipiravir, as a purine analog compound that has been used as an antiviral drug, shows a less
198 binding affinity to the 3-Cl protease receptor and spike glycoprotein receptor when compared to
199 remdesivir. According to (Wang et al., 2020), favipiravir was effective in high doses to inhibit viral
200 replication. On the other side, remdesivir, as an adenosine analogue that inhibits viral replication, was
201 known to have a high affinity for proteases compared to spike glycoprotein receptors (Eweas et al.,
202 2021). The results of this study showed that α -farnesen, β -sesquifelandren and Ar-curcumin were more
203 potent than favipiravir and remdesivir because these three compounds showed better binding affinity
204 at two different receptors because they had lower free energy values.

205 According to the potency of α -farnesen, β -sesquifelandren and Ar-curcumin compared to
206 favipiravir and remdesivir, this study analyzed the physicochemical properties of these three
207 compounds to be developed as new drug candidates following Lipinski's rules (Chen et al., 2020). This
208 rule was used to predict the drug likeness of a chemical compound with its physico-chemical
209 properties for the oral route of administration. According to the Lipinski rule, Rule of 5 (RO5), a drug-
210 like compound should have a molecular weight of not more than 500, log P value not more than 5,
211 hydrogen bond donors not more than 5 and hydrogen bond acceptors not more than 10.
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Table 3. The Physico chemical properties of the compound

Compound	Molecular weight	Hydrogen bond donor	Hydrogen bond acceptors	Log P
β -sesquifelandren	204,19	0	0	5,608
Ar-curcumin	202,17	0	0	5,9
α -farnesen	204,19	0	0	6,286
Favipiravir	157,03	3	5	-0,934
Remdesivir	602,23	5	14	1,961

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The data in Table 3 showed that none of the potential herbal compounds followed Lipinski's rule regarding log P, which must be less than 5. The log P value indicated the distribution coefficient of compounds in fat and water, which plays an important role in drug adsorption. However, in several cases related to natural materials, the log P value may not suit Lipinski requirements. According to (Chen et al., 2020), if the log P value does not suit the requirements but the other parameters suit the requirements, then the compound could still be accepted, taking into account its other properties.

The results of the adsorption, distribution, metabolism, and excretion test of the three most potent compounds and comparators are shown in Table 4.

Table 4. ADMET calculation

Compound	CaCO-2 (log cm/second)	VD (l/kg)	CYP3A4 inhibitor	Total clirens (mL/minute/ kg)	Rat Oral Toxicity (mg/kg)
β -sesquifelandren	-4,492	5,514	0,588	15,405	0,028
Ar-curcumin	-4,375	4,736	0,512	12,748	0,025
α -farnesen	-4,565	5,502	0,321	14,162	0,016
Favipiravir	-5,244	0,653	0,005	8,141	0,522
Remdesivir	-5,611	1,817	0,514	6,052	0,719

225 Notes :

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CaCO-2: adenocarcinoma cell line, VD: volume distribution, CYP3A4; sitokrom isoenzim 3A4

228 Absorption of compounds in the intestine was an important parameter to determine the adsorption
229 of compounds. The permeability of human colon adenocarcinoma cells was one of the most frequently
230 used approaches to estimate drug in vitro in log cm/second units. A compound was said to have a good
231 value if it had a unit value greater than -5.15 (Dong et al., 2018). From the results of the search for
232 potential herbal compounds and comparators, it appears that the herbal compounds have good
233 absorption in the intestine as indicated by a value of > -5.15 . The antivirus drug even has a value less
234 than -5.15 and was declared not good. This was supported by in vivo test data on patients regarding the
235 absorption of remdesivir and favipiravir. According to (Humeniuk et al., 2021), the bioavailability of
236 remdesivir intravenously is 100%, and it was formulated for intravena uses. (Gülhan et al., 2022)
237 found that the absorption of favipiravir in 52% of Covid-19 patients who consumed favipiravir at a
238 loading dose of 3200 mg on the first day and a maintenance dose of 1200 mg on days 2 to 5 had not
239 reached drug concentrations above $20\mu\text{g/mL}$.

240 The distribution of a compound in the body was determined theoretically by measuring the volume
241 of distribution expressed in the prediction of the compound binding to plasma proteins, the amount of
242 distribution in the fluid, and the amount of absorption in the fluid. A compound was considered to
243 have a good volume of distribution if it was in the range of 0.04-20 l/kg (Dong et al., 2018). From the
244 calculation results it appears that the herbal compounds and antivirals drug had a good distribution in
245 the body.

246 Drug metabolism in the body was generally divided into phase I (oxidative) and phase II
247 (conjugative), with the contribution of cytochrome P450 enzymes in the liver. To predict ADMET, the
248 approach of a compound could be used as a substrate or inhibitor of various isoenzymes, one of which
249 was the CYP3A4 isoenzyme, which was most commonly found in the liver and was responsible for
250 metabolism (Dong et al., 2018). The calculation results showed that all compounds were not potential
251 as substrates, so it could be concluded that the compounds were not toxic to the liver.

252 Total clearance was an excretion parameter that was commonly determined as a pharmacokinetic
253 parameter. According to (Dong et al., 2018), the prediction of total clearance was expressed in units of
254 ml/minute/kg with a range of numbers, and if it was greater than 5, it was declared good. The results
255 showed that all compounds had good total clearance values.

256 Rats acute toxicity was one of the toxicity parameters used to determine the safety of the test
257 compound. In the ADMET lab2 prediction, it is expressed as a range of numbers with conditions 0-0.3
258 indicating good results, 0.3-0.7 indicating medium results, and 0.7-1 indicating poor results. From the
259 data, it showed that the 3 potential compounds had good value when compared to favipiravir and
260 remdesivir which tend to be toxic. Clinically, favipiravir and remdesivir had toxicity to the liver,
261 gastrointestinal tract, respiratory tract, kidneys, and heart, which until now, according to (Fan et al.,
262 2020), was still being investigated.

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264 CONCLUSION

265 It can be concluded that α -farnesen, β -seskuifelandren and Ar-curcumin in ginger in sufficient
266 concentrations had the potential to be developed as oral corona antivirals. α -farnesen is the most
267 potential compound because it has the best interaction among the other three compounds.

268

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271

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