Biointerface Research in Applied Chemistry
Platinum Open Access Journal (ISSN: 2069-5837)

Article
Volume 11, Issue 5, 2021, 12869 - 12876
https://doi.org/10.33263/BRIAC115.1286912876

Shogaol, Bisdemethoxycurcumin, and Curcuminoid: Potential Zingiber Compounds Against COVID-19

Indah Rakhmawati Afrida [1, 2, *], Fatchiyah Fatchiyah [1], Nashi Widodo [1], Mohamad Amin [3], Muhammad Sasmito Djati [1]

[1] Biology Department, Faculty of Mathematics and Natural Sciences, Brawijaya University, Malang 65145, East Java, Indonesia
[2] Biology Education Program, Faculty of Teacher Training and Education, University of Muhammadiyah Jember, Jember, East Java, Indonesia
[3] Biology Department, Faculty of Mathematics and Natural Sciences, State University of Malang, Malang 65145, East Java, Indonesia
* Correspondence: indahrakhmawatiafrida@unmuhjember.ac.id;

Scopus Author ID 56403414400
Received: 22.12.2020; Revised: 18.01.2021; Accepted: 24.01.2021; Published: 31.01.2021

Abstract: Coronavirus disease (COVID-19) is a global pandemic in the world. Some treatments, including vaccines and potential drugs, are still developed. This study investigated the bioactive compounds of *Zingiber officinale*, *Kaempferia rotunda*, and *Curcuma zedoaria* as a potential inhibitor for ACE2 and RdRP proteins. Molecular docking was used for screening the bioactive compounds as ACE2 and RdRP inhibitors. Shogaol (CID 5281794), zingerone (CID 31211), chalcone (CID 637760), Ar-turmerone (CID 558221), bisdemothxycurcumin (CID 5315472), and curcuminoid (CID 101341353) interacted with angiotensin-converting enzyme receptor-2/ACE2 (PDB ID 2xd3) and RNA dependent RNA polymerase/RdRP (PDB ID 6xqb), then analyzed using Discovery studio v.19 program. Shogaol, zingerone, chalcone, ar-turmerone, bisdemethoxycurcumin, and curcuminoid bound to ACE2 and RdRP protein in some active sites. Zingerone, chalcone, and ar-turmerone are attached to the ACE-2 and then RdRP protein in similar active sites, suggesting those compounds stabilize the complex ACE-2 and RdRP protein. Shogaol interacted with the RdRP and ACE2 protein amino acid residues in the Shogaol-RdRP+ACE2 complex, indicating shogaol blocks the RdRP-ACE2 interaction. Then, bisdemethoxycurcumin and curcuminoid change the binding sites of ACE2 and RdRP protein when both compounds are bound to RdRP protein. This study suggested that shogaol, bisdemethoxycurcumin, and curcuminoid are potential drugs for COVID-19 prevention.

Keywords: ACE2; COVID-19; curcuma; ginger; RdRP protein.

1. Introduction

Severe acute respiratory coronavirus syndrome-2 (SARS-COV-2) caused Coronavirus disease (COVID-19) that spread rapidly worldwide [1–3]. December 2020, more than 82 million cases have been confirmed. COVID-19 killed more communities on a daily or weekly basis on cardiovascular disease, diabetes, and other diseases [3]. Several drugs and treatments involving vaccines are still undergoing to prevent SARS-COV-2 infections. The SARS-COV-2 is a single strand RNA with 14 open reading frames (ORFs) that code 27 structural and non-structural proteins. The SARS-COV-2 protein is divided into two crucial structures, 5'-end encoding non-structural proteins and 3'-end encoded structural proteins. The non-structural protein of SARS-COV-2 proteins is multi domain protein/pro-poli protein, chymotrypsin like,

helicase and RNA dependent RNA polymerase (RdRP). The structural protein of SARS-COV-2 protein included spike surface glycoprotein, envelope, nucleocapsid, and matrix [4–7].

The infection mechanism of SARS-COV-2 in humans has been reported. The spike glycoprotein of SARS-COV-2 is attached to the receptor of angiotensin-converting enzyme-2 (ACE2) in an epithelial cell on nasopharynx tissue [1, 8–10]. Then the coronavirus released their RNA and replicated and produced the other genome coronavirus. The RdRP protein is a non-structural protein that played a crucial role in genome replication [6, 7]. The RdRp is associated with nsp7 and nsp8 as Auxiliary factors to synthesize viral RNA [5]. Two possible drug target designs for preventing COVID-19 infection, the first drug targeted to the viral directly and the second targeted to the human cell infection [4, 11–13].

The viral entry of SARS-CoV-2, immunity enhancement, and non-structural protein inhibitor seems to be a possible target for antiviral drug discovery. Malin *et al*. [14] reported that remdesivir and chloroquine effectively control the 2019-nCoV infection *in vitro*. Plant compounds and their derivates are often used to minimize toxins and promote healing [15]. Ginger rhizome has the largest polyphenol component, consisting of gingerol and shogaol, flavonoids [16–18]. S *et al*. [19] reported that 10-shogaol content inhibits ACE, Tiring *et al*. [16] showed 6-shogaol and 8-shogaol activity blocks cJun NH2-terminal Kinase protein. *Kaempferia*, another *Zingiberace* with pharmacological function, including anti-cancer, anti-inflammatory, antimicrobial, Anticholinesterase, and antioxidant anti-allergic, and anti-injury properties [20]. *Curcuma zedoaria* or white turmeric is a plant found in the Indonesian region in the Zingiberaceae family. White turmeric is an annual plant that has antimicrobial properties [21]. This study predicted the bioactive compounds from *Zingiber officinale*, *Kaempferia* rotunda, and *Curcuma zedoaria* to inhibit the interaction between ACE2-RdRP SARS-COV-2.

2. Materials and Methods

2.1. Ligand and protein data mining.

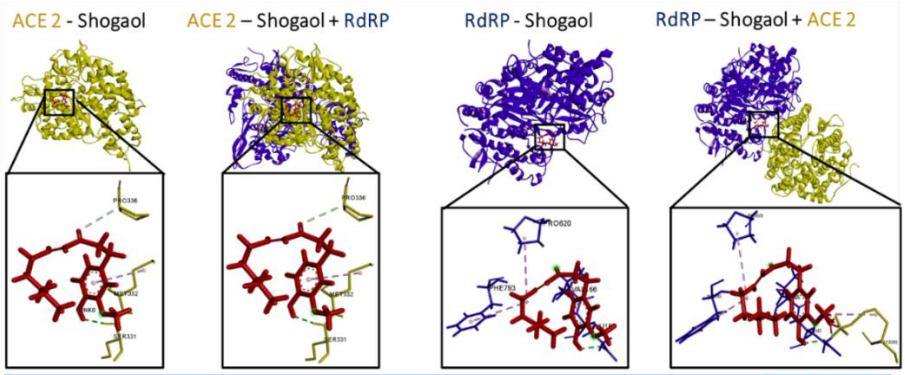
The bioactive compounds from *Zingiber officinale* including Shogaol (CID 5281794) and ZINGERONE (CID 31211), *Kaempferia rotunda* (chalcone, CID 637760), and *Curcuma zedoaria* involved Ar-turmerone (CID 558221), Bisdemothxycurcumin (CID 5315472), and Curcuminoid (CID 101341353) were downloaded from PubChem database. Angiotensin-converting enzyme receptor-2 and RdRP proteins were taken out from PDB database with ID 2xd3 and 6xqb, respectively.

2.2. Molecular docking.

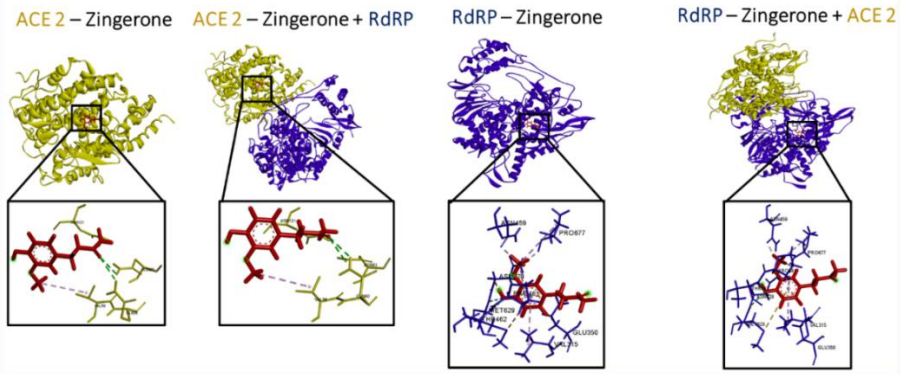
Ligands were prepared using PyRx 0.8 [22], ACE-2, and RdRP proteins were prepared by Discovery studio v.19 software. Ligands and Proteins were docked and analyzed using the Hex 8.0.0 Software. Energy calculations are performed with each of these servers. The 3D visualization of the docking results is viewed using the Discovery Studio v.19 programs to analyze amino acid residues, energy bonds, van der Waals forces, and hydrogen bonds formed [15, 16].

3. Results and Discussion

The complex protein of ACE 2-shogaol and ACE2-shogaol+RdRP showed interaction in three amino acid residues in the same residues involved LEU333, THR334, and PRO336 (Figure 1). Both of those complex performed binding energy -170.76 cal/mol and -455.56 cal/mol, respectively. Shogaol interacted with RdRP protein in several binding sites: ARG553, VAL792, PHE793, PRO620, LYS621, VAL166 ASP161 proved binding energy -261.07 cal/mol. The RdRP-Shogaol-ACE2 revealed some active site residues ARG553, VAL792, PHE793, PRO620, LYS621, VAL166, ASP161, and LYS353 with binding energy -596.83 cal/mol (Figure 1). Similar active sites of ACE 2-shogaol and ACE2-shogaol+RdRP suggested that shogaol stabilize ACE-2 and RdRP protein interaction. In RdRP-Shogaol+ACE2 complex protein, shogaol bound in between RdRp and ACE2 receptor. The binding energy of complex ACE2-shogaol+RdRP and RdRP-Shogaol+ACE2 were lower than ACE 2-shogaol and RdRP-shogaol.



Complex Interaction	Residues	Category	Binding energy (cal/mol)
ACE 2 - Shogaol	LEU333, THR334, PRO336	Hydrophobic	-170.76
ACE 2 – Shogaol + RdRP	LEU333, THR334, PRO336	Hydrophobic	-455.56
RdRP - Shogaol	ARG 553, VAL792, PHE793, PRO620, LYS621, VAL166, ASP161	Hydrophobic	-261.07
RdRP – Shogaol + ACE 2	ASP161, VAL792, PHE793, PRO620, VAL166, ARG553, LYS621, LYS353	Hydrophobic	-596.83



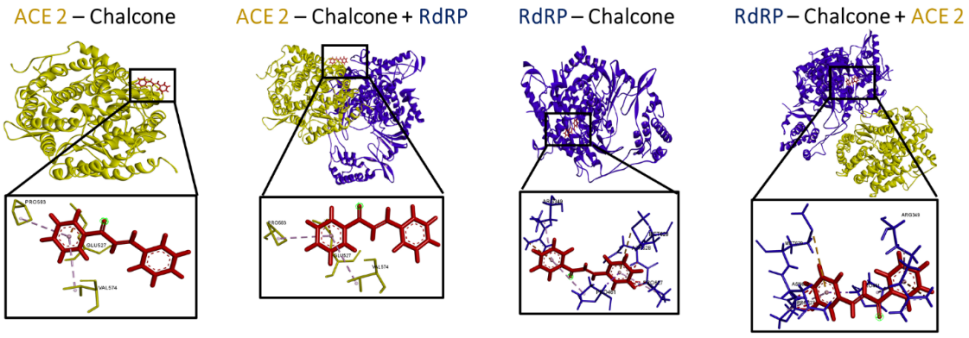
Complex Interaction	Residues	Category	Binding energy (cal/mol)
ACE 2 – Zingerone	THR122, ASN121, ASN63, THR125	Hydrophobic	-189.27
ACE 2 – Zingerone + RdRP	THR122, ASN63, ASN121, THR125	Hydrophobic	-592.02
RdRP – Zingerone	MET629, GLU 350, VAL 315, ARG349, THR319, SER318, LEU460, PRO461, ASN459, PRO667	Hydrophobic	-195.88
RdRP – Zingerone + ACE 2	MET639, PRO461, VAL315, GLU350, SER318, THR319, ARG349, LEU460, ASN459, PRO677	Hydrophobic	-601.26

Figure 1. The interaction among shogaol and zingerone with ACE2 and RdRp SARSCOV2 protein. The yellow color is ACE2 protein, the blue color is RdRp SARSCOV2 protein, and the red color showed ligands.

Zingerone bound to ACE 2 protein at THR122, ASN121, ASN63, and THR12 of ACE2. ACE 2-Zingorone and ACE 2-Zingorone+RdRP performed binding energy -189.27 cal/mol and -592.02 cal/mol. RdRP-Zingerone showed amino acid residues:MET629,

GLU350, VAL315, ARG349, THR319, SER318, LEU460, PRO461, ASN459, PRO667 with binding energy -195.88 cal/mol. The RdRP-Zingerono+ACE 2 complex proved binding sites, including MET639, PRO461, VAL315, GLU350, SER318, THR319, ARG349, LEU460, ASN459, and PRO677, with binding energy -601.26 cal/mol (Figure 1). Zingerone interacted with RdRP in different amino acid residues, suggesting zingerone moving out when ACE2 interacted with RdRP.

ACE 2-Chalcone interaction formed amino acid residue in PRO583, ASN580, GLY575, LYS553, GLN542, VAL574, GLU527 energy -210.13 cal/mol. Complex ACE 2-Chalcone-RdRP showed amino acid residues PRO583, ASN580, VAL573, GLN524, LYS553, GLY575, and GLU527 with energy -586.36cal/mol. Interaction RdRP-Chalcone released amino acid residues ASN459, ASN628, PRO627, PRO677, MET629, PRO461, SER318, ARG349, THR319, LEU460, and MET626 energy -221.61cal/mol (Figure 2). RdRP-Chalcone-ACE 2 showed some residues, PRO627, THR462, MET629, ASN628, SER318, ARG349, THR319, ASN459, PRO677, LEU460, PRO461, and MET626 and resulted in binding energy -603.25 cal/mol (Figure 2).



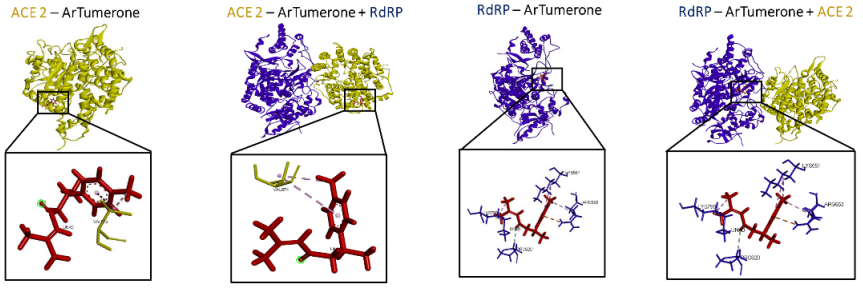
Complex Interaction	Residues	Category	Binding energy (cal/mol)
ACE 2 – Chalcone	PRO583, ASN 580, GLY575, LYS553, GLN524, VAL574, GLU527	Hydrophobic	-210.13
ACE 2 – Chalcone + RdRP	PRO583, ASN 580, VAL574, GLN524, LYS553, GLY575, GLU527	Hydrophobic	-586.36
RdRP – Chalcone	ASN459, ASN628, PRO627, PRO677, MET629, PRO461, SER318, ARG349, THR319, LEU460, MET626	Hydrophobic	-222.61
RdRP – Chalcone + ACE 2	PRO627, THR462, MET629, ASN628, SER318, ARG349, THR319, ASN459, PRO677, LEU460, PRO461, MET626	Hydrophobic	-603.25

Figure 2. The interaction between chalcone with ACE2 and RdRp SARSCOV2 protein. The yellow color is ACE2 protein, the blue color is RdRp SARSCOV2 protein, and the red color showed ligands.

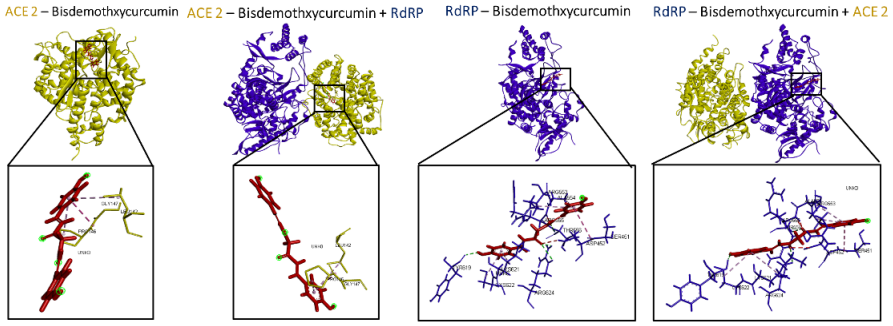
Ar-turmerone interacts with the ACE2 receptor in VAL574, while the ACE2-Ar-turmerone complex binds to RdRP protein, showing VAL574 and PRO260. The other complexes were RdRP-Ar turmerone and RdRP-Ar tumerone+ACE2, both of them proved the same residues (Figure 3). Bisdemothyxcurcuminoid formed a complex with ACE2 receptor and RdRP protein in the same active sites, indicating that bisdemothyxcurcuminoid stabilize the interaction between ACE2 and RdRP protein. Interestingly, bisdemothyxcurcuminoid change the binding sites of ACE2 and RdRP protein when bisdemothyxcurcuminoid associated with RdRP protein.

Curcuminoid also stabilized the interaction between ACE2 and RdRP protein when curcuminoid blocked ACE2 protein, even though the curcuminoid showed different amino acid residues in ACE2-curcuminoid and ACE2-curcuminoid+RdRP complexes. The RdRP-curcuminoid protein complex proved various active sites with RdRP-curcuminoid+ACE2. Remarkably, RdRP-curcuminoid+ACE2 performed a higher number of active sites and changed the ACE2-RdRP complex protein's binding sites. The ligand-protein complex's binding site and three-dimensional structures revealed that bisdemothyxcurcuminoid and

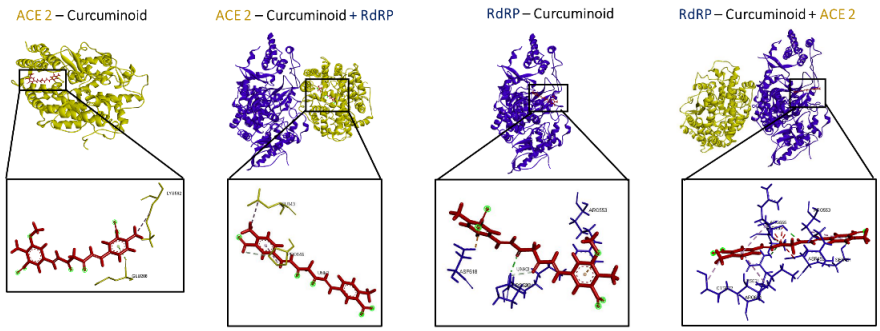
curcuminoid might have the ability to be antiviral through RdRP blocking. According to the binding energy data, the complex protein of turmeric compounds-ACE2-RdRP was lower than the turmeric compound's interaction with ACE2 or RdRP protein. The lower binding sites were supported by the high number of hydrogen and hydrophobic interactions.



Complex Interaction	Residues	Category	Binding energy (cal/mol)
ACE 2 – ArTumerone	VAL574	Hydrophobic	-223.1
ACE 2 – ArTumerone + RdRP	VAL574	Hydrophobic	-645.5
RdRP – ArTumerone	PRO620 ARG553 LYS551, ARG553, LYS798, LYS551	Hydrogen Bond Electrostatic Hydrophobic	-223.1
RdRP – ArTumerone + ACE 2	PRO620 ARG553 LYS551, ARG553, LYS798, LYS551	Hydrogen Bond Electrostatic Hydrophobic	-646.3



Complex Interaction	Residues	Category	Binding energy (cal/mol)
ACE 2 – Bisdemothxycurcumin	LEU142, PRO146	Hydrophobic	-237.4
ACE 2 – Bisdemothxycurcumin + RdRP	LEU142, PRO146	Hydrophobic	-604.5
RdRP – Bisdemothxycurcumin	THR556, ARG624, TYR619, ARG555 SER451, ASP452, ARG553, ALA554, LYS621, CYS622 ARG555, ASP452	Hydrogen Bond Hydrophobic Unfavorable	-276.4
RdRP – Bisdemothxycurcumin + ACE 2	THR556, ARG624, TYR619, ARG555 SER451, ASP452, ARG553, ALA554, LYS621, CYS622 ARG555, ASP452	Hydrogen Bond Hydrophobic Unfavorable	-553.5



Complex Interaction	Residues	Category	Binding energy (cal/mol)
ACE 2 – Curcuminoid	GLU208 LYS562	Other Hydrophobic	-296,91
ACE 2 – Curcuminoid + RdRP	PRO146 LEU143, PRO146	Hydrogen Bond Hydrophobic	-584.0
RdRP – Curcuminoid	LYS621, PRO620 ARG553, ASP618	Hydrogen Bond Electrostatic	-298.18
RdRP – Curcuminoid + ACE 2	SER451, ARG555, THR556, ARG624 CYS622, ARG553, ARG555, LYS621 ARG555, ASP452	Hydrogen Bond Hydrophobic Unfavorable	-564.8

Figure 3. The interaction among turmeric compounds (Ar Tumerone, Bisdemothxycurcumin, and curcuminoid) with ACE2 and RdRp SARSCOV2 protein. The yellow color is ACE2 protein, the blue color is RdRp SARSCOV2 protein, and the red color showed turmeric compounds as ligands.

Viral entry and genome replications are the crucial targets for preventing the COVID-19 from spreading. The RNA-dependent RNA polymerase (RdRp) is a non-structural protein-

12 (nsp12), which was the most important protein for coronavirus replication/transcription complex [6, 7, 9, 23, 24]. Previous studies reported curving the COVID-19. Some bioactive such as remdesivir, favipiravir, and penciclovir as antiviral agents were used to blocking the RdRp virus [25–28]. In this case, we found compounds from Zingiber officinale is Shogaol and Zingerone, *Kaempferia rotunda*, Chalcone and *Curcuma zedoaria* involved Ar-turmerone, bisdemothxycurcumin, and curcuminoid. Those bioactive compounds interacted both on ACE2 and RdRP proteins. We found those compounds are binding with the amino acid residues in various active sites both of RdRP and ACE-2 receptor. A recent study revealed that Zn is a stabilizing cofactor of RdRP protein bound to His295, Cys301, Cys306, and Cys310 of RdRP residues. Zink ion is also attached to RdRP protein in the finger domain, Cys487, His642, Cys645, and Cys646 [5, 29]. In this study, potential compounds involved shogaol, bisdemethoxycurcumin, and curcuminoid were discovered as RdRP inhibitors. A previous study explored and informed that ribavirin, sofosbuvir, baloxavir, dasabuvir, galidesivir, pimodivir, and beclabuvir an antiviral drug with RdRP as targeted protein [7]. Some polyphenols reported as COVID-19 prevention, resveratrol, curcumin, and emodin inhibit the interaction between ACE-2 and spike glycoprotein through spike glycoprotein. The other compounds bound to spike glycoprotein were naringenin, epigallactocathecin gallate, hesperidin, tangeretin, and curcumin derivates [23, 27].

The complex protein of bioactive compounds in ginger, *Kaempferia*, and turmeric with ACE2 and RdRP were lower than the complex of bioactive compounds-ACE2 or bioactive compounds-RdRP. The binding energy caused close interaction in ligand-protein interaction. Some interactions contributing to the binding energy were hydrogen bonds, hydrophobic interaction, electrostatic, and van der Waals [30–32]. Binding energy correlated with binding affinity, depending on H-bond and altering one or more atoms in compounds that interacted with the protein target. Besides that, the H-bond mixed with disulfide bonds decreased the binding affinity in ligand-protein interaction [33]. Hydrogen bonds and hydrophobic interaction were important to enhance the optimum drug design [30–33]. In the current study, the molecular docking among bioactive compounds of ginger, Kaempfera, and turmeric with ACE2 and or RdRP protein was dominant with hydrophobic interactions. The number hydrogen bond was only showed in turmeric complex with ACE2 and or RdRP protein. A previous study reported that the interaction of S2 protein of SARSCOV2 and ACE2 promoted hydrophobic interaction, which caused hydrophilic residues in this area, releasing hydrogen in water molecules and promoting hydrogen electrostatic bonds [34, 35]. In the current study, the complex bioactive constituents revealed a lowering binding affinity of ACE2-RdRP proteins, greatly decreasing the COVID-19 infectious.

4. Conclusions

Virtual screening of bioactive compounds from *Zingiber officinale, Kaempferia rotunda*, and *Curcuma zedoaria* suggested shogaol, bisdemothxycurcumin, and curcuminoid have a potential activity to reduce the effect of ACE2 -RdRp SARSCOV2 protein interaction through RdRP inhibition.

Funding

This research was supported by Universitas Muhammadiyah Jember 2020.

Acknowledgments

The authors also thank Dewi Ratih Tirto Sari for technical assistance throughout this work.

Conflicts of Interest

No conflict of interest declared.

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