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Research Article

In Silico Phytochemical Compounds Screening of *Allium sativum* Targeting the Mpro of SARS-CoV-2

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ABSTRACT

The global pandemic of coronavirus disease is still widely spread across the world causing catastrophic effect in both human life and global economy. By the end of year 2021, it has caused a total of 5.437.636 deaths across the world. Indonesia has rich plant biodiversity including medicinal plants that may be used for combating the virus. One of the commonly used medicinal plants comes from *Allium* species and it has been proved to have antiviral activity. Conducting an *in silico* study, we screened bioactive compounds that came from *Allium sativum* to fight against coronavirus through the inhibition of 3CL-Pro, one of the major protease that have an active role for viral replication. Molecular docking of compounds from *Allium sativum* to 3CL-Pro resulting in the discovery of 5 compounds that have the best binding affinity to 3CL-Pro, which are squalene, 1,4-dihydro-2,3-benzoxathiin 3-oxide, 1,2,3-propanetriyl ester, trans-13-octadecenoic acid and methyl-11-hexadecenoate with binding affinity of -7, -6.5, -5.9, -5.7 and -5.6 kcal/mol, respectively. It is very likely that these compounds can be candidates for therapeutic agents and these candidates need to be studied further.

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INTRODUCTION

The global pandemic of coronavirus disease, especially caused by the outbreak of SARS-CoV-2 virus, is still widely spread across the world causing catastrophic effect in not only human life but also in global economy.[1,2] Coronavirus disease pandemic started in the late December 2019 and according to WHO, by the end of 2021, the total of cases and death incident were 288.867.634 and 5.437.636 across the world, respectively.[3] This virus can spread rapidly through aerosol, such as cough and sneezing making the spread of virus uncontrollable.[4] Furthermore, based on the severity, it can cause ARDS, respiratory failure, septic shock or multiple organ failure.[5] Therefore, there is a need to find an alternative treatment to fight these virus infections.

SARS-CoV-2 has proteolytic processing enzymes (proteases) that act as a main regulator of the virus replication activity and the blocking of this activity were proved to hinder the replication of the virus in human.[6-8] These 2 proteases are papain-like protease (PL-Pro) and 3-chymotrypsin (C)-like cysteine protease (3CL-Pro).[6,7] They cleave CoV-encoded poyproteins (pp1a and pp1b) into nonstructural proteins (nsps) that is needed for viral replication. While PL-Pro cleave into 4 nsps (nsp1-nsp4), 3CL-Pro can cleave into 7 nsps (nsp5-nsp11).[6,7] 3CL-Pro is a more desirable target to be inhibited than PL-Pro because the formation of double-membrane vesicles is coded by nsps cleaved by 3CL-Pro[6] and 3CL-Pro inhibitors are not toxic to human.[9] Taken together, 3CL-Pro is a potential target for SARS-CoV-2 therapy.

In the past two years, the world has been racing to find and develop the appropriate and effective treatment for SARS-CoV-2 diseases and one of them is by the utilization of medicinal plants.[10] Many studies reported the beneficial of medicinal plants for combating virus-derived diseases.[11] The antiviral properties of medicinal plants such as *Sambucus nigra*, *Withania somnifera*, *Sylibum marianum* dan *Moringa oleifera* have been proved to be effective against human virus such as HIV,[12] Hepatitis C,[13] HSV-1[14] and influenza.[15] These evidences suggested that it is also very likely for these plants to have bioactive compounds against SARS-CoV-2 virus. Therefore, medicinal plants can be utilized as one of the alternatives for treatment of SARS-CoV-2.

Indonesia is one of many countries that have rich plant biodiversity including medicinal plants.[16] One of the commonly used medicinal plants comes from *Allium* species. The bioactive compounds of *Allium* species have been reported to have many antiviral properties. For examples, *Allium cepa* has been proved to completely remove the viral activity of Newcastle Disease Virus (NDV).[17] *Allium* plants also showed to have anti-adenoviral activity which can prevent diseases, including respiratory illness, gastroenteritis and neurologic disease.[18] *Allium sativum* is a well-known functional food for its immunomodulatory and antiviral properties.[19] It has been reported that *Allium sativum* has been have antiviral activities against influenza virus, HSV-1, HSV-2 and human rhinovirus type 2.[20] In this *in silico* study, we observed and screened various plant-derived compounds (phytochemicals) of *Allium sativum* especially against 3CL-Pro as an effort to discover a new anti-COVID drug through molecular docking.

METHODS

3CL-Pro (Mpro) protein preparation

The 3CL-Pro (6WTT)[21] was obtained from RCSB PDB database. Preparation of the protein was done

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by removing the water and ligand molecule from the protein with PyMOL software for further analysis.

Sample preparation

A total of 20 compounds from *Allium sativum* were selected (shown in Table 1). The 3D structure and canonical SMILES from each peptide were available from PubChem database (pubchem.ncbi.nlm.nih.gov). These compounds were then termed as ligands. All ligands were then had its conformational energy minimized using PyRx 0.8 software. Furthermore, the 3CL-Proteinase (6WTT)[21] was obtained from RCSB PDB database. Preparation of the protein was done by removing the water and ligand molecules from the protein with PyMOL software for further analysis.

Drug-likeness analysis

Analysis of drug-likeness was performed on the selected compounds using the Lipinski Rule tools on SCFBIO web server. For the compounds to be categorized as a drug-like molecules, they have to meet at least 2 rules out of five Lipinski rule. Lipinski rule of five consisted of 1) molecular mass more than 500 Dalton; 2) high lipophilicity (LogP) more than 5; 3) hydrogen bond (HBD) more than 5; 4) hydrogen bond acceptors (HBA) more than 10; and 5) molar refractivity (MR) between 40 and 130.

Antiviral activity probability

The selected 20 bioactive compounds were predicted for its antiviral activity with PASS web server (http://way2drug.com/PassOnline/). Pa (Potential activity) score > 0,3 (medium confident) was set as standard. Moreover, Pi (Probability) score should be lower than Pa score for the compound to be able to work properly in the human body.

Molecular docking

The docking of protein and ligand was done using AutoDock Vina software that was integrated in PyRx 0.8. Top five ligands that have the lowest binding affinity value were picked and used for further analysis. First of all, the grid docking of 3CL-Pro was set to have center coordinate (Å) of X = -15,9; Y 30,8; and Z = 11,9. Then the dimension (Å) of X = 67.2; Y = 92.3; and Z = 37.9 was also set. Molecular interaction between protein and ligands was investigated with BIOVIA Discovery Studio 2019. Then the docking results were visualized in 3D using PyMOL software by looking at binding position of protein and ligand.

RESULTS AND DISCUSSION

Drug-likeness and antiviral activity analysis

Firstly, all 20 selected bioactive compounds from *Allium sativum* were analyzed for its possibility to be drug-like molecules using Lipinski rule of five. As mentioned earlier, Lipinski rule of five consist 5 rules which bioactive compounds can be categorized as drug-like molecules if they did not violate more than 2 of the rules. Based on the analysis on all of the 20 bioactive compounds, they all fulfilled the Lipinski rule of five requirements and were categorized as drug-like molecule (Table 1).

Next, we analyzed the potential of each bioactive compounds as an antiviral agent online with PASS web server. One can be predicted as a potential antiviral agent when the Pa score of the component is more than 0.3. Based on the analysis on all of the bioactive compounds, they all showed Pa score more than 0.3 with squalene for the highest Pa score (0.817) and 1,2,3-propanetriyl ester for the lowest Pa score (0.402) (Figure 1). This means that all 20 bioactive compounds were predicted as potential antiviral agents. However, further *in vitro* and *in vivo* study need to be done to examine the antiviral property of the bioactive compounds.

Molecular docking results

Molecular docking analysis was performed between ligand and target protein, in this case 3CL-Pro, to find out the stability level of interaction formed by ligand-protein complex. The interaction stability level was shown by the value of binding affinity. The lower the binding affinity, the more stable the interaction, the higher the inhibition activity performed by the ligand towards the protein target. A study by Kneller *et al.* (2020), showed that M^{Pro} protease was harboring a catalytic area containing asparagine (Asn), glutamine (Gln) and proline (Pro) as its residual amino acids.[22] As shown in Table 2, all 20 bioactive compounds can act as 3CL-Pro ligand and form complex with it through the interaction with 3CL-Pro active site showed by the prediction value of its binding affinity. However, only top five bioactive

Table 1: Drug-likeness prediction (Lipinski Rule of Five).

No.	Compounds	Lipinski Rule of Five				
		MW	HBD	HBA	LogP	MR
1	Squalene	410,000	0	0	10,605	140,060
2	1,4-Dihydro-2,3-benzoxathiin 3-oxide	168,000	0	2	2,246	43,212
3	1,2,3-propanetriyl ester	227,000	0	9	-0,714	44,606
4	trans-13-Octadecenoic acid	282,000	1	2	6,109	87,088
5	Methyl-11-hexadecenoate	268,000	0	2	5,417	82,234
6	9,12-Hexadecadienoic acid, methyl ester	266,000	0	2	5,193	82,140
7	Oleic Acid	282,000	1	2	6,109	87,088
8	Hexanedioic acid	146,000	2	4	0,716	33,740
9	Pentadecanoic acid	242,000	1	2	5,162	73,330
10	cis-Vaccenic acid	282,000	1	2	6,109	87,088
11	13-Tetradecen-1-ol acetate	254,000	0	2	5,027	77,617
12	Tridecanoic acid, 12-methyl-, methyl ester	242,000	0	2	4,716	73,024
13	11,14-Octadecadienoic acid, methyl ester	294,000	0	2	5,973	91,374
14	Hexadecanoic acid, methyl ester	270,000	0	2	5,641	82,328
15	Dodecanoic acid	200,000	1	2	3,991	59,480
16	Methyl tetradecanoate	242,000	0	2	4,860	73,093
17	n-Hexadecanoic acid	256,000	1	2	5,552	77,948
18	Tetradecanoic acid	228,000	1	2	4,772	68,714
19	Dodecanoic acid, methyl ester	214,000	0	2	4,080	63,860
20	Oleanitrile	263,000	0	1	6,547	85,065

Table 2: Ligand docking result to 3CL-Pro.

No.	Compounds	Binding Affinity (kcal/mol)
1	Squalene	-7
2	1,4-Dihydro-2,3-benzoxathiin 3-oxide	-6.5
3	1,2,3-propanetriyl ester	-5.9
4	trans-13-Octadecenoic acid	-5.7
5	Methyl-11-hexadecenoate	-5.6
6	9,12-Hexadecadienoic acid, methyl ester	-5.5
7	Oleic Acid	-5.5
8	Hexanedioic acid	-5.4
9	Pentadecanoic acid	-5.2
10	cis-Vaccenic acid	-5.2
11	13-Tetradecen-1-ol acetate	-5.1
12	Tridecanoic acid, 12-methyl-, methyl ester	-5.1
13	11,14-Octadecadienoic acid, methyl ester	-5
14	Hexadecanoic acid, methyl ester	-4.9
15	Dodecanoic acid	-4.9
16	Methyl tetradecanoate	-4.9
17	n-Hexadecanoic acid	-4.7
18	Tetradecanoic acid	-4.6
19	Dodecanoic acid, methyl ester	-4.6
20	Oleanitrile	-4.6

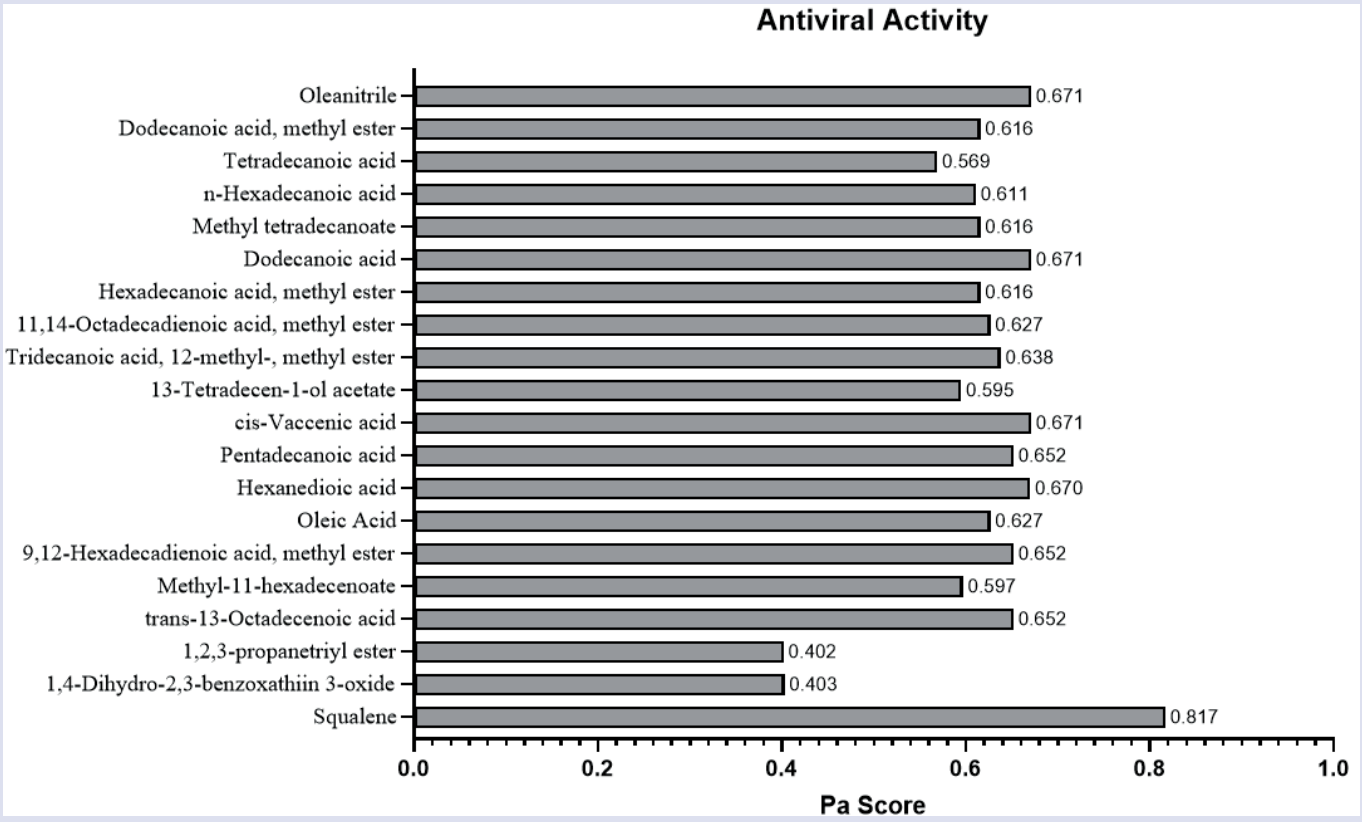

Figure 1: Antiviral activity probability of *Allium sativum* compounds.

compounds with the lowest binding affinity were further analyzed for bond interaction with 3CL-Pro which consist of hydrogen bond and hydrophobic interaction. Those five bioactive compounds were squalene, 1,4-Dihydro-2,3-benzoxathiin 3-oxide, 1,2,3-propanetriyl ester, trans-13-Octadecenoic acid and Methyl-11-hexadecenoate with binding affinity of -7, -6.5, -5.9, -5.7 and -5.6 kcal/mol, respectively.

The importance of M^{Pro} protease as one of the SARS-CoV-2 protease and its role for viral replication has been mentioned before.[26] The coding region of this protease is exceptionally conservative and not found in another host including human.[23] Moreover, M^{Pro} structure has been a common and well-published information.[24] Consequently, this protease coding region became a well-liked target for the development

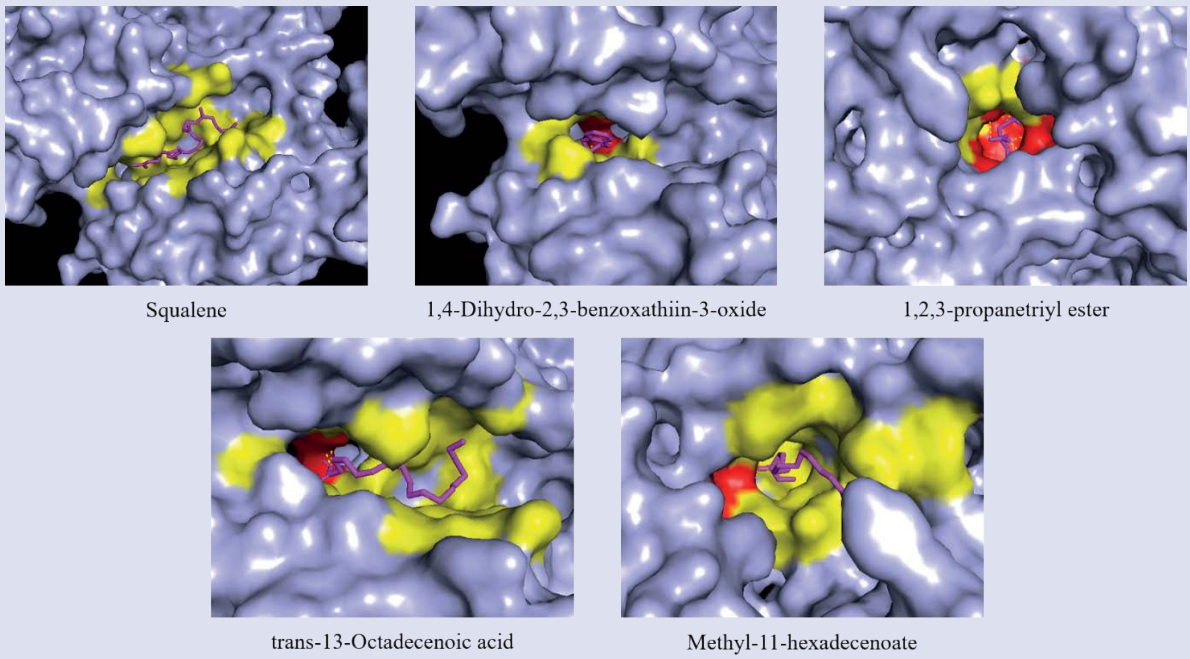

Figure 2: Visualization of protein-ligand docking. Protein, ligand, hydrogen bond and hydrophobic interaction were colored by light blue, magenta, red and yellow, respectively.

Table 3: The interaction of top 5 *Allium sativum* ligands with 3CL-Proteinase.

No	Compound	Binding Affinity (kcal/mol)	Position of Chemical Bond	
			Hydrogen Bond	Hydrophobic Interaction
1	Squalene	-7	-	Phe103, Phe134, Pro184, Tyr101, Arg105, Lys88, Val35
2	1,4-Dihydro-2,3-benzoxathiin 3-oxide	-6.5	Arg105, Ser81	Lys90, Val35
3	1,2,3-propanetriyl ester	-5.9	Gln83, Asn180, Asn84, Thr201, Val202, His246	-
4	trans-13-Octadecenoic acid	-5.7	Ser81	Phe103, Pro184, Tyr101, Val35
5	Methyl-11-hexadecenoate	-5.6	Asn84, Asn180	Ile249, Phe294, Val202, Pro293, His246, Ile200, Pro132, Pro108

of antiviral drug combating SARS-CoV-2.[25] Based on the information of M^{Pro} structure, researchers developed not only peptidomimetic but also non-peptidomimetic as M^{Pro} inhibitor.[26] Hsu and colleagues successfully developed a peptidomimetic compound, TG-0205221, and had been tested to have antiviral activity by binding with M^{Pro} protease through 10 hydrogen bonds and 1 covalent bond resulting in strong interaction with the protease.[27] While developing peptidomimetic for SARS-CoV-2, medicinal plants have also made an appearance as one of the alternatives for the virus treatment. The non-peptidomimetic molecules, such as bioactive compounds, contained in plants were reported to have inhibitory effect on M^{Pro} protease.[28-31]

Table 3 shows the interaction of compounds and 3CL-Pro. Squalene, which has the best binding affinity (-7 kcal/mol), interacts only hydrophobically with 3CL-Pro (Figure 2). It binds with both of the 3CL-Pro domain (Domain A and B). On domain A, squalene binds hydrophobically with amino acids which are, Tyr101, Val35, Lys88, Phe103 and Arg105. While on domain B, squalene binds hydrophobically with amino acids, Phe134 and Pro184. Interestingly, even without hydrogen bond, squalene can have low binding affinity value with only hydrophobic interaction with 3CL-Pro, making this compound a potentially good inhibitor of SARS-CoV-2 entry and replication and a therapeutic agent for COVID-19.

1,4-Dihydro-2,3-benzoxathiin 3-oxide on the other hand, interacts with 3CL-Pro by both hydrogen binding and hydrophobic interaction resulting in 1,4-Dihydro-2,3-benzoxathiin 3-oxide is being held to the 3CL-Pro with binding affinity of -6.5 kcal/mol (Figure 2). Similar to the previous compound, 1,4-Dihydro-2,3-benzoxathiin 3-oxide also binds with both of the 3CL-Pro domain. On domain A, amino acid Ser81 binds via hydrogen bond with 3CL-Pro, while the benzene ring of this compound binds hydrophobically with amino acids Lys90 and Val35. On the other hand, on domain B, this compound has hydrogen bond with amino acid Arg105 of 3CL-Pro.

The compound trans-13-Octadecenoic acid has binding affinity with 3CL-Pro with the value of -5.7 kcal/mol (Figure 2). It forms protein-ligand complex with both hydrogen and hydrophobic interactions. It forms one hydrogen bond on domain A with amino acid Ser81. The others are hydrophobic interactions which takes place on both domains A and B. On domain A, trans-13-Octadecenoic acid interacts hydrophobically with Tyr101 and Val35. On the other hand, it interacts with amino acids Phe134 and Pro184 on domain B.

Different with squalene, 1,2,3-propanetriyl ester only have hydrogen bonds to keep the protein-ligand complex together with binding affinity of -5.9 kcal/mol (Figure 2). On domain A, 1,2,3-propanetriyl ester binds with amino acids Gln83, Asn84 and Asn180. While on domain B, this compound binds with amino acids Thr201, Val202 and His246.

Similar to trans-13-Octadecenoic acid, Methyl-11-hexadecenoate is also dominantly bound to 3CL-Pro by hydrophobic interactions

(Figure 2). On domain A, Methyl-11-hexadecenoate forms hydrogen bonds with Asn84 and Asn180. On the other hand, on domain B, all of the interactions made with 3CL-Pro are hydrophobic interactions. This compound interacts with amino acids Ile249, Phe294, Val202, Pro293, His246, Ile200, Pro132 and Pro108. Taken together, all of these interactions create a binding affinity of -5.6 kcal/mol.

As described above, these 5 compounds have the lowest binding affinity to 3CL-Pro compared to the other compounds. Interestingly, each of these compounds have different interaction with amino acids on 3CL-Pro. Originally, the docking of these compounds is intended to find the best candidate compound to be used as an alternative treatment of COVID-19. Based on this in silico study, these 5 candidates can be further analyzed on its biological activity and pathway to prevent COVID-19 entry and duplication on human body.

CONCLUSION

In this study, the bioactive compounds in *Allium sativum* are subjected to Lipinski's rule of five, molecular docking analysis and chemical interactions to 3CL-Pro. Out of all 20 compounds, 5 compounds namely squalene, 1,4-Dihydro-2,3-benzoxathiin 3-oxide, 1,2,3-propanetriyl ester, trans-13-Octadecenoic acid and Methyl-11-hexadecenoate have the best binding affinity towards 3CL-Pro. However, to prove the actual activity of these compounds towards 3CL-Pro, further study *in vitro* and *in vivo* needed to be done.

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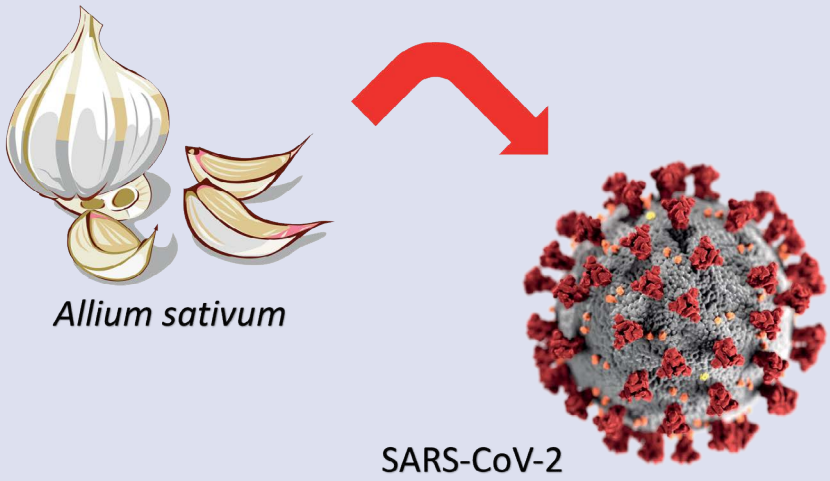
GRAPHICAL ABSTRACT



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Rahadian Zainul has completed a Bachelor of Educational Chemistry in IKIP Padang, then continued his studies and obtained a Master of Chemistry at Universitas Andalas, and earned a Doctoral Chemistry degree at Universitas Andalas. He is a researcher on the design and modification of copper oxide for inactivation SARS-CoV-2 by stimulated indoor lights and a researcher on the design and modification of copper oxide by computation approach with DFTB+. He is also the Head of Cambiotics Research Center, Universitas Negeri Padang. The author has published 41 manuscripts in Scopus-indexed journals and also 8 h-index.

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