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¹ Potential of tilapia (*Oreochromis niloticus*) viscera bioactive peptides as antiviral for SARS-CoV-2 (COVID 19)

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Abstract. Pandemic SARS-CoV-2 (COVID-19) is a severe problem in the world today. The SARS-CoV-2 virus contains protease and glycoprotein spike, which was used infection and development. The RBD (Receptor Binding Domain) of the glycoprotein Spike (RBD-S) can bind to the ACE2 receptor (Angiotensin Converting Enzyme-2) on the Domain protease (PD) (PD-ACE2) of the host cell causing virus infection. This study aimed to evaluate the potential of bioactive peptides from tilapia viscera hydrolysate as an antiviral peptide to attempt a simulated docking with four protein target virus COVID 19. The research was conducted by molecular docking using the PyRx software. Selected protein targets were SARS-CoV-2 protease (GDP ID: 6LU7), SPIKE COVID 19 (PDB ID: 6LVN), ACE2 (GDP ID: 6VW1), and deubiquitinase inhibitors block the SARS virus replication (PDB ID: 3E9S). The formed binding affinity was represented as a docking score. The results showed that both the Asp-Trp and Val-Tyr peptides were potential as SARS-CoV-2 antiviral, with an affinity strength equal to chloroquine and favipiravir. The Asp-Trp and Val-Tyr peptides could bind to all four receptor proteins target on the active side. Therefore, it potentially inhibits the virus sticking to proteins target that results in inhibition of virus replication. Generally, the Asp-Trp and Val-Tyr peptides of tilapia viscera hydrolysate are potential as an alternative antiviral peptide to medicate the infections and replication of COVID-19.

1. Introduction

Aquaculture waste such as viscera contain highly protein and unsaturated fatty acids [1]. fish viscera can be utilized as a raw material for hydrolysate proteins [2]. It can minimize environmental and health issue and reduce the economic impact [3]. One of the efforts to utilize fish waste is using hydrolysis technology. Hydrolysis technology breaks down complex bonds into simple bonds in the form of bioactive peptides using enzymes, acids, and bases [4]. Bioactive peptides are specific protein that possess a health benefit. Proteins in the whole form have weak bioactivity, whereas hydrolyzed proteins will increase biological activity because it has been separated from the complex bonds [5].



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1
Bioactive peptides have potential effects as antihypertensive, antioxidants [6], opioid antagonists, antibacterial [7], antithrombotic, and immunomodulatory [8]. Peptides extracted from food proteins are able to maintain blood pressure, weight balance [9], inhibit the specific endopeptidase activity of Prolin, boost the immune system, inhibit blood platelet aggregation, inhibit HIV proteinases and oxidation processes, possess antibacterial and antimicrobial activity, ion binding and transport minerals and improve nutritional food values [10, 11]. Previous research has shown the numbers and diversities of amino acid profiles of tilapia viscera hydrolysate [12, 13], which potentially to be developed as a bioactive peptide-based pharmaceutical agent candidate.

The new Coronavirus, SARS-CoV-2 or COVID 19, became a worldwide outbreak, spreading across the continent of Asia, Europe, the Middle East, Africa, and America covering more than 100 countries. The pandemic of the SARS-CoV-2 virus attracts rapid challenges in finding drugs candidate that correspond to the molecular characteristics of the SARS-CoV-2 virus. Researchers have found characteristics of the glycoprotein spike structure, which plays an essential role in the SARS-CoV-2 viral infection [14, 15, 16]. The glycoprotein of SARS-CoV-2 shows a slight difference in the primary structure compared to the beta coronavirus, SARS-CoV (due to mutation) so it needs new antiviral drugs candidate [17].

The Spike of glycoprotein SARS-CoV-2 contains Domain Binding receptors (RBD) that drive the virus towards the protein receptors target, and leads to the connection of the trimeric spike proteins to S1 and S2, facilitating membrane fusion and virus infections through endocytosis [18]. The angiotensin-converting-enzyme 2 (ACE2) is a receptor that is targeted to the glycoprotein spike SARS-CoV-2 [19] [20]. Therefore, RBD and glycoprotein spikes are targeted protein receptors to inhibit SARS-CoV-2 virus infection (COVID 19). It is noted that many compounds have been traced to RBD Spike glycoprotein [21] or with molecular docking model as screening for candidate drugs. However, the results show limited candidates to be prospective medications due to threats of adverse effects [22, 23, 24].

Despite the glycoprotein spike, ACE2 is another candidate that is suitable for drug targets to prevent virus infections. Drugs candidate address the spike binding site to bind the spike-RBD glycoprotein [18] [25]. The binding site of the Ligan-ACE2 is recognized as a domain protease (PD), which plays a role in the trimeric Spike glycoprotein structure as an essential step in virus infections [26, 27]. Therefore, the inhibitory effect of some compounds against these receptors suggests protecting the virus identifications.

Protease inhibitors are developed as drug candidates to cease the life cycle of viruses [28]. Beta coronavirus uses proteases to break the structural proteins during the formation of viruses in the host cell. Protease inhibitors have been developed to prevent spreading viruses such as HIV-AIDS, MERS, and SARS [29]. Many drug candidates have also been screened with promising results to treat SARS-CoV-2 as a drug repurposing, such as lopinavir (the drug HIV-AIDS) [24, 30]. Studies on finding the best protease inhibitors to address the SARS-CoV-2 infections were getting increase by using a in silico model with a sophisticated crystal structure of domain-inhibitor proteases [31, 32]. This approach needs further examine to find best candidates for an antiviral agent that is more precise, effective, and has minimal side effects.

To inhibit the rate of Covid-19 pandemic, the Government of the Republic of Indonesia took the policy to use the drug Chloroquine and Favipiravir. The aim of this research was to evaluate the potential of bioactive peptides from tilapia viscera hydrolysate as an antiviral peptide to attempt a simulated docking with four protein target virus COVID 19, namely SARS-CoV-2 protease (GDP ID: 6LU7), SPIKE SARS-CoV-2 (GDP ID: 6LVN), RBD-ACE2 complex (GDP ID: 6VW1), and deubiquitinase inhibitors blocks of SARS virus replication (GDP ID: 3E9S) compared with chloroquine and favipiravir.

2. Materials and method

Tilapia viscera was obtained from PT Aquafarm Nusantara, Semarang Industrial Estate, Indonesia. Viscera cleaned with water, and a defatting process was carried out. Furthermore, the hydrolysis process was carried out using the alcalase enzyme (Sigma-Aldrich No. 126741) [12].

Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) (Thermo Scientific Dionex Ultimate 3000) equipped RSLCnano with Microflow meter was used to characterize Tilapia viscera hydrolysate. LC-HRMS analysis was conducted using Model LC-HRMS manufacturer. Chromatography separation is carried out using the analytical Column Hypersil GOLD aQ 50 × 1 mm × 1.9 μ particle size. Two solvents are prepared, 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B). Analytical Flow rate 40 ml/min for 30 minutes, column temperature 30 °C. HRMS Analysis uses Thermo Scientific Q Exactive (Full scan at 70,000 resolution, data-dependent MS2 at 17,500 resolution, run time 30 minutes). Chromatogram data obtained processed by processing data software: Compound discoverer with mzCloud MS/MS library. The second stage is to predict the biological activity of hydrolysate compounds using PASS online by including canonical SMILE

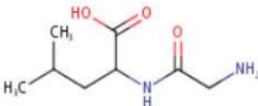
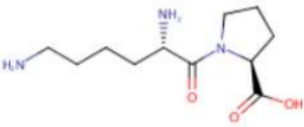
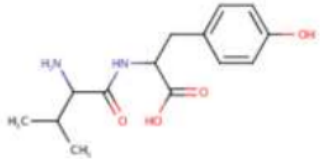
The study of molecular docking was selected as a tool for the screening affinity binding of the bioactive peptides contained in the tilapia viscera hydrolysate. The four target proteins of SARS-CoV-2, namely the SARS-CoV-2 protease (GDP ID: 6LU7), SPIKE COVID 19 (GDP ID: 6LVN), ACE2 (GDP ID: 6VW1), and deubiquitinase inhibitors blocks of SARS virus replication (GDP ID: 3E9S). All simulated computing was performed on the Windows 10 operating system, the Intel Core i5-8th Gen as a processor with 4 GB of RAM. Molecular docking studies include activity predictions with online PASSES, docking simulations, RMSD calculations, and visualization interactions between proteins and peptides performed using PyRx and Biovia Discovery Studio Visualizer 2019. The molecular docking results describe the affinity indicated by the docking score and the binding interaction of each compound on the four target proteins. Compounds are analyzed for the drug-likeness Lipinski and toxicity prediction using swissADME and Pro-Tox II.

3. Results and discussion

3.1 Results

The results of LC-HRMS analysis, seven peptides were found in the tilapia viscera hydrolysate (Table 1).

Table 1. Bioactive peptides from the tilapia viscera hydrolysate

No	Bioactive Peptides	Chemical structure
1	Gly-Leu (GL) CID 92843	
2	Lys-Pro (KP) CID 171204	
3	Val-Tyr (VY) CID 4065033	

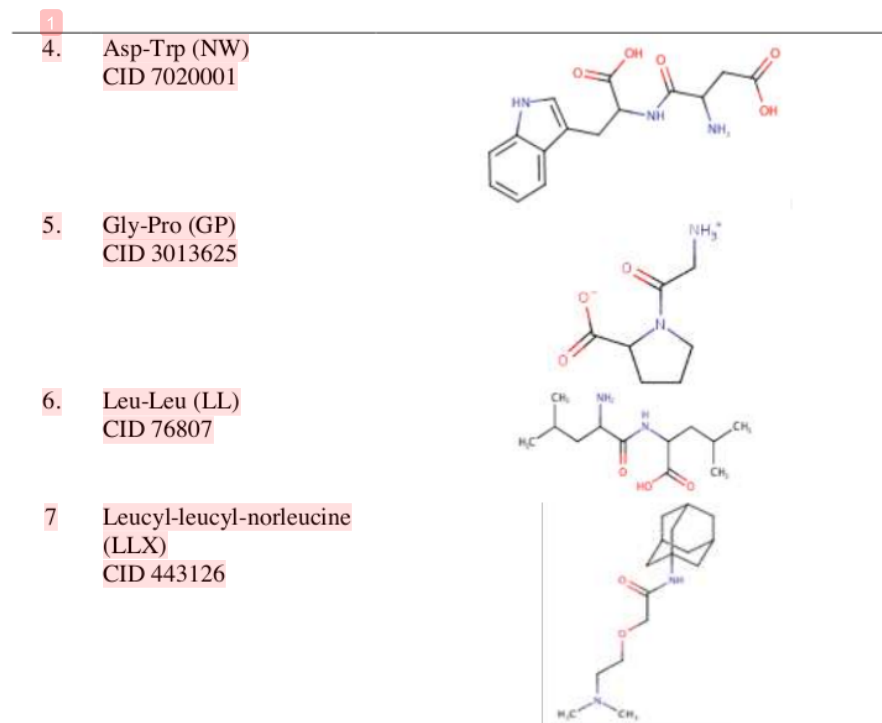


Table 2 showed the potential of the seven different peptides detected from tilapia viscera hydrolysate as an antiviral, compared with chloroquine and favipiravir.

Table 2. Prediction analysis of bioactive peptides from tilapia viscera hydrolysate as antiviral using PASS online

Bioactive Peptides	Simian immuno-deficiency virus proteinase inhibitor		Antiviral (Adeno-virus)		Antiviral (Influenza)		3C-like protease (Human corona-virus) inhibitor		Viral entry inhibitor		Antiviral (Influenza A)		Antiviral (Rhino-virus)		Antiviral	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
Asp-Trp (7020001)	0.68	0.00	0.36	0.05	0.35	0.07	0.27	0.05	0.25	0.03	0.27	0.07				
Glycyl-L-leucine (92843)	0.82	0.00	0.53	0.00	0.39	0.05	0.30	0.03	0.23	0.06	0.34	0.02	0.41	0.08	0.20	0.10
Glycyl-L-proline (3013625)	0.39	0.06	0.34	0.06	0.49	0.03			0.24	0.05	0.45	0.01	0.54	0.01		
Lys-Pro (171204)	0.35	0.08	0.30	0.09	0.62	0.01			0.23	0.06	0.48	0.00	0.55	0.01		
Leucyl-leucyl-norleucine (443126)	0.85	0.00	0.55	0.00	0.56	0.02	0.31	0.02	0.21	0.13	0.38	0.01	0.44	0.06	0.27	0.05
Leu-Leu (76807)	0.89	0.00	0.59	0.00	0.51	0.02	0.34	0.01	0.23	0.06	0.37	0.01	0.42	0.08	0.27	0.05

Val-Tyr (7009555)	0,82	0,00	0,37	0,04	0,43	0,04	0,33	0,01	0,21	0,11	0,31	0,03	0,31	0,23	0,29	0,04
Chloroquine (2719)																
Favipiravir (492405)	0,34	0,09	0,27	0,11	0,66	0,01	0,25	0,08							0,45	0,01

In order to knowing the potency of seven peptides from tilapia-viscera hydrolysate against four receptor targets, namely: protease SARS-CoV-2 (GDP ID: 6LU7), SPIKE COVID 19 (GDP ID: 6LVN), RBD-ACE2 (GDP ID: 6VW1), and deubiquitinase inhibitors block the SARS virus replication (PDB ID: 3E9S) the molecular docking was conducted and compared with chloroquine and Favipiravir as a comparative control. The docking results provide a variation of the D-G binding energy (gibbs energy) represented by the docking score between the receptors (Figure 1).

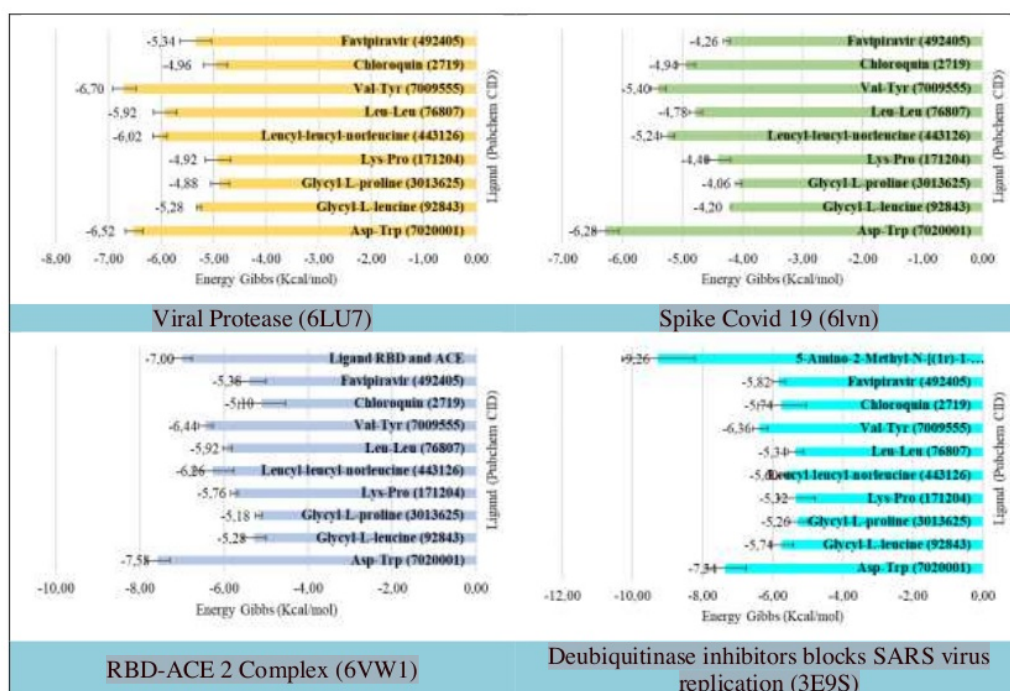


Figure 1. Binding energy between seven bioactive peptides with four receptor targets

Figure 1 showed that the Asp-Trp and Val-Tyr peptides have lower gibbs energy than chloroquine and favipiravir. Lower binding affinity energy may represent a more potent inhibitory activity against viral infections. The results visualizations of Asp-Trp and Val-Tyr peptides with all four receptors showed that the Asp-Trp and Val-Tyr bioactive peptides are able to bind the receptors target on the expected side (Figure 2, 3, 4, and 5).

In addition, we try to distinguish if the Asp-Trp and Val-Tyr peptides can serve as drugs (drug-likeness) based on Lipinski's rules [33]. The toxicity predictions of the Asp-Trp, Val-Tyr, chloroquine, and favipiravir peptides were analyzed using Pro-Tox II [34]. The toxicity power is assessed in LD50 in the unit of mg/kg body weight. Drug-likeness lipinski analysis and toxicity prediction can be seen in Table 3.

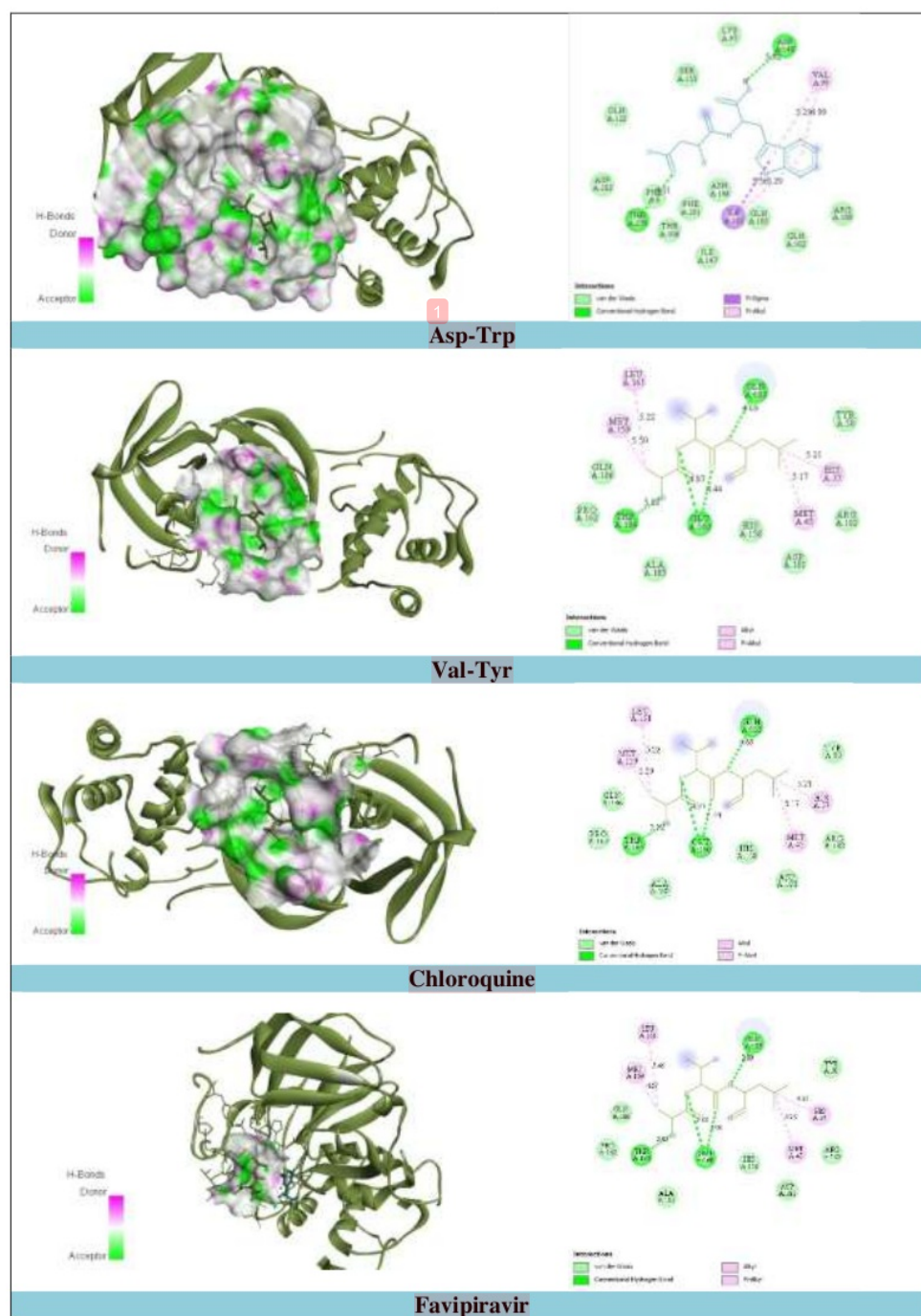


Figure 2. Binding interaction profile of Asp-Trp and Val-Tyr peptides from tilapia viscera hydrolysate compared to chloroquine and favipiravir on protease domain of SARS-CoV-2.

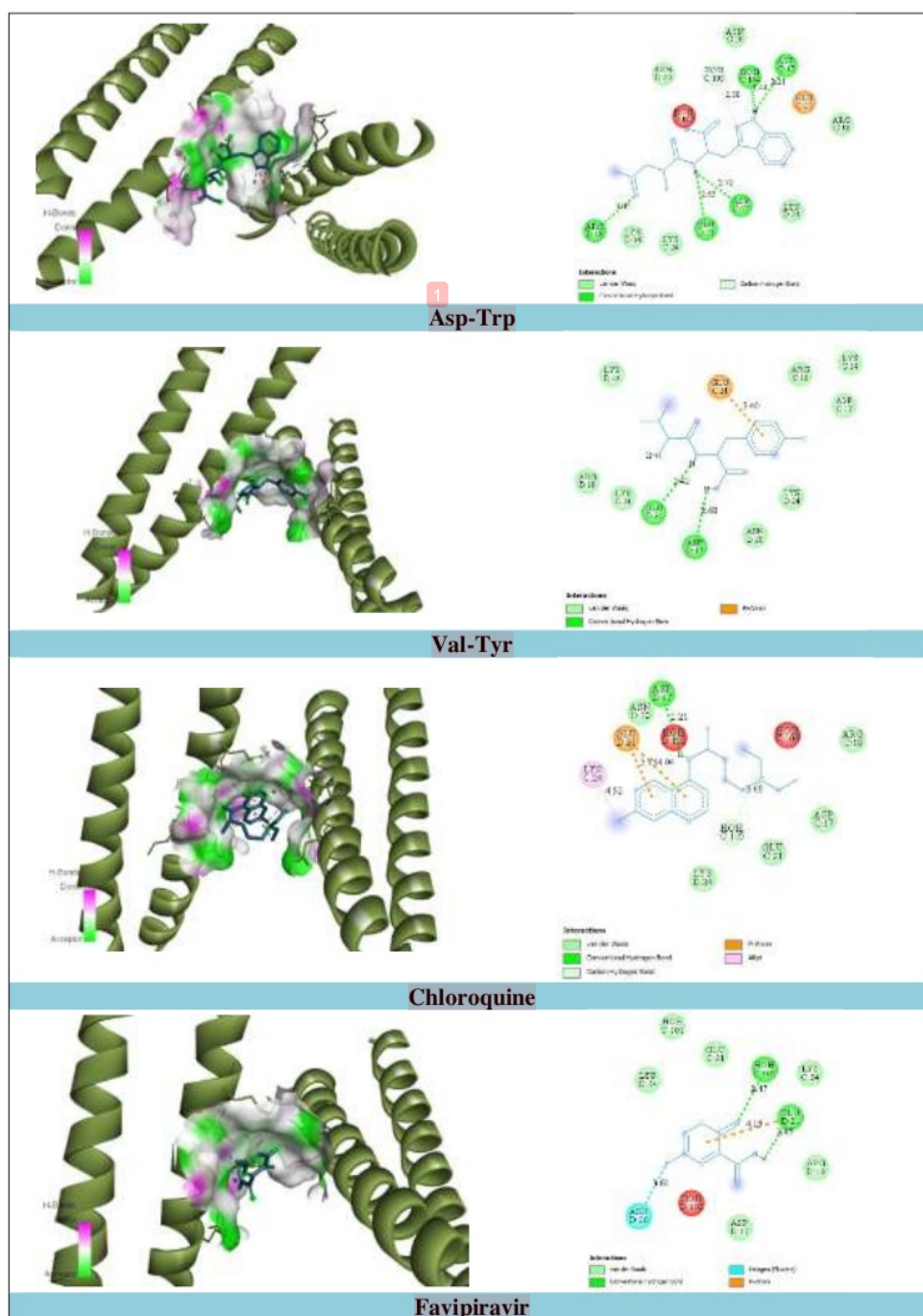


Figure 3. Binding interaction profile of Asp-Trp and Val-Tyr peptides from tilapia viscera hydrolysate compared to chloroquine and favipiravir on spike SARS-CoV-2

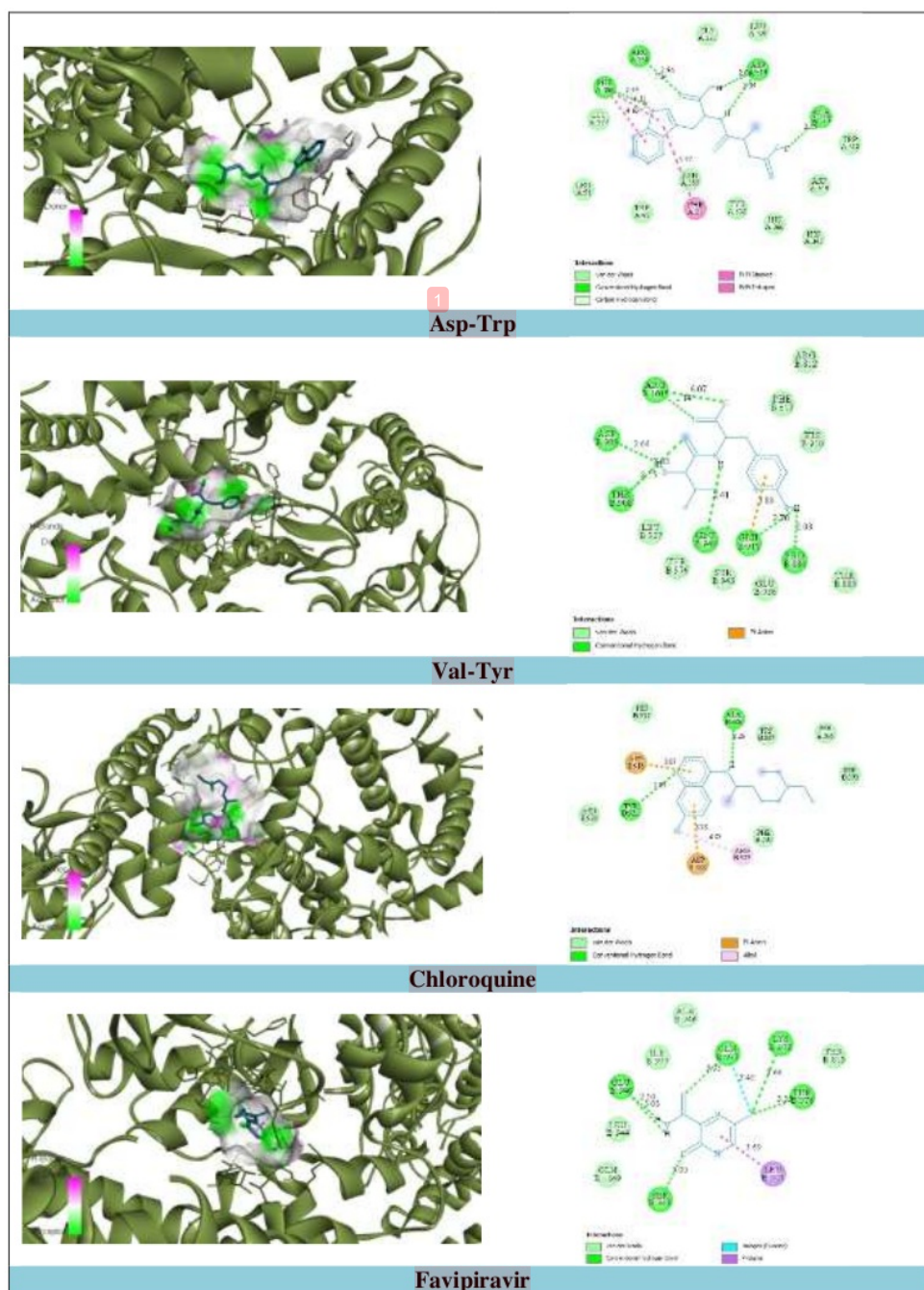


Figure 4. Binding interaction of Asp-Trp and Val-Tyr peptides of tilapia viscera hydrolysate compared to chloroquine and favipiravir on RBD-ACE2 complex

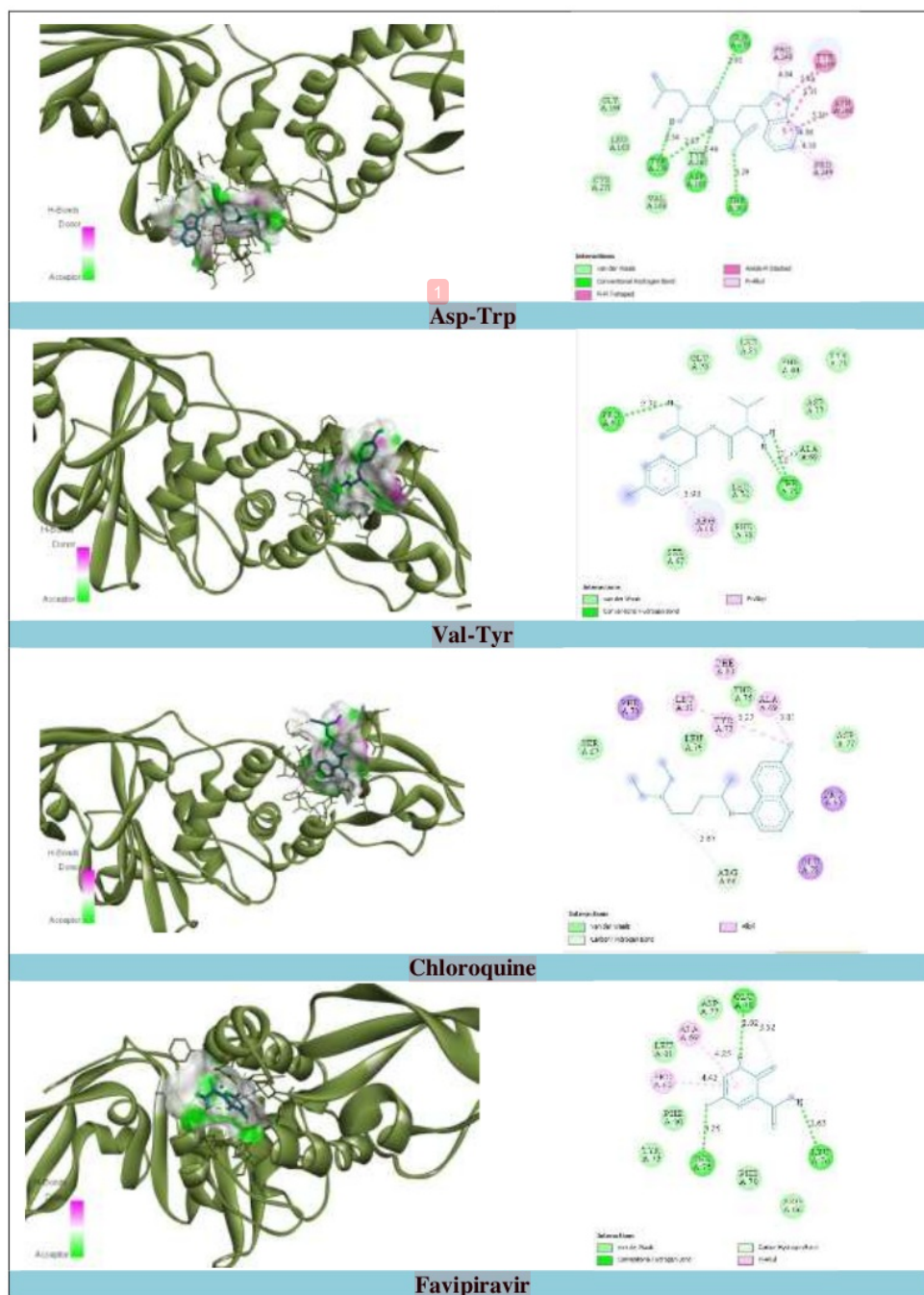


Figure 5. Binding interaction profile of Asp-Trp and Val-Tyr peptides from tilapia viscera hydrolysate compared to chloroquine and favipiravir on deubiquitinase inhibitors blocks SARS virus replication (3E9S).

Table 3. Drug-likeness lipinski analysis and toxicity prediction

Peptides	Asp-Trp (CID 7020001)	Val-Tyr (CID 7009555)	Chloroquine (CID 2719)	Favipiravir (CID 492405)
Molecular Weight < 500 Dalton (g/mol)	319.31	280.32	319.87	157.10
High Lipophilicity (expressed as Log P < 4.15)	-0.54	0.61	3.20	-1.30
Hydrogen Bond Donors < 5	5	4	1	2
Hydrogen Bond Acceptors < 10	6	5	2	4
Molar refractivity 40-130	81.36	74.56	97.41	32.91
Prediction of LD50 (mg/kg) /	10500 /	5300 /	860 /	3000 /
Toxicity Class	VI	VI	IV	V

3.2 Discussion

Table 2 showed activity prediction analysis using PASS online, seven peptides have the potential for antiviral activity compared to control (Chloroquine and Favipiravir). PASS online could be used to predict biological activities. The highest Pa values group Probability in Active (Pa) types. The predicted compound can be proven as an analog of the registered pharmacological agent. It is a compound with a value of Pa > 0.7, possibly having a rather high experimental activity, but the compound has the possibility of any known pharmacological agent. Compounds with a range of 0.5 < Pa < 0.7, possess moderate activity, but their compounds will be less similar to pharmacological agents. The value of Pa < 0.5, it is likely to have lower activity, but the level of likeness to the compound with known compounds is low, it indicates a new chemical class structure and has biological activity that needs to be examined [35].

Chloroquine is a pharmaceutical agent used as an antiparasmodial (antimalaria) [36]. Chloroquine is able to suppress TNF- α and IL-6 production in rheumatoid arthritis [37] and is used in autoimmune therapies such as lupus [38]. The mechanism of action of chloroquine is penetrating to the cells and concentrated in the acidic cytoplasm. Chloroquine increases vesicles pH in macrophages or antigen-presenting cells, thus acting as immunosuppressants by affecting the immune response to antigen [39] [40].

In addition to being antimalarial and immunosuppressant, chloroquine and hydroxychloroquine are potentially used as antiviral [41]. Chloroquine has an antiviral effect on prevention and therapeutic mechanisms [42]. In vitro study showed the inhibition of chloroquine to infectious SARS of Cov-2 [43]. Chloroquine hinders virus replications, and interacts with angiotensin-converting receptor enzyme 2 (ACE2). The interaction of chloroquine with ACE 2 can inhibit the virus bonding with the receptors, so the virus cannot adhere to the infected receptors, and so that the infection process can be prevented [44]. However, the use of chloroquine clinics needs further research, as it has not been successfully proven in clinical trial for infected patients with hereditary diseases [45]. Furthermore, Favipiravir is antiviral agent as RNA polymerase inhibitor [46]. It can inhibit the RNA Virus synthesis [47]. Favipiravir showed antiviral potency to SARS-CoV2 [48]. It is significantly medicated SARS-CoV2 in term of in terms of disease spreading and virus clearance [49].

Figure 2 showed a bonding visualization between the Asp-Trp and Val-Tyr peptides with proteases of the virus. The docking simulation results in the Asp-Trp, Val-Tyr, and chloroquine peptide bonds in the viral protease, not on the active side. The amine group of Favipiravir binds to the active site of proteases with hydrogen bonds, namely glutamine (GLN A:183), Treonina (THR A:184), and Glutamate (A:160). The bonding distance ranges from 2.83 to 2.89 Å. The SARS-CoV-2 virus has an amine group (-NH₂) in its structure, as it is a single strand RNA virus [50]. This amine group can be a target of antiviral compounds.

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Figure 3 showed a bonding visualization between the Asp-Trp and Val-Tyr peptides with Spike SARS-CoV-2. The docking simulation results in the peptide bonds of Asp-Trp, Val-Tyr, Chloroquine, and Favipiravir on the SARS-CoV-2 spike, on the active side using hydrogen bonds. The NH₂ cluster of Asp-Trp binds to spike SARS-CoV-2, on Aspartate (C:17 and D:17), Glutamate (D:21). At the same time, the Asp-Trp carboxylic group binds to spike SARS-CoV-2, on Arginine (D:18). The NH₂ cluster of Val-Tyr binds to spike SARS-CoV-2, on Glutamate (D:21). At the same time, the carboxyl Asp-Trp cluster binds to spike SARS-CoV-2, at Aspartate (D:17). The NH₂ of Chloroquine binds to spike SARS-CoV-2, at Aspartate (D:17). The NH₂ cluster of favipiravir binds to spike SARS-CoV-2, on Glutamate (D:21). CoVs is a positive-strand RNA virus with a crown-like appearance, as it has a glycoprotein spike on the surface [51]. Spike glycoproteins on the virus's surface can guide the virus towards ACE2 receptor proteins [52]. The Asp-Trp and Val-Tyr peptides from the extract of the tilapia viscera hydrolysate are able to bind to the SARS-CoV-2 spike so it cannot bind to the target protein receptors.

Figure 4 showed binding visualization between Asp-Trp and Val-Tyr peptides with the RBD-ACE2 complex. The docking simulation results in the position of the peptide bonds of Asp-Trp, Val-Tyr, chloroquine, and favipiravir on the RBD-ACE2 complex, located on the active side using hydrogen bonds. The NH₂ cluster of Asp-Trp binds to the RBD-ACE2 complex, at Aspartate (A:319), Phenylalanine (A:356). At the same time, the carboxyl Asp-Trp cluster binds to the RBD-ACE2 complex, on Alanine (A:317), Aspartate (A:319), and Arginine (A:358). The NH₂ cluster of Val-Tyr binds the RBD-ACE2 complex, in Threonine (B:908) and Glutamate (B:940). The ester group of the Val-Tyr binds to the RBD-ACE2 complex at Arginine (B:1045).

The amide group of the Val-Tyr binds to the RBD-ACE2 Complex in Threonine (B:908). The hydroxyl group of the Val-Tyr binds to the RBD-ACE2 complex on Glutamate (B:911) and Proline (B:884). The NH₂ cluster of chloroquine binds to the RBD-ACE2 complex on Alanine (B:886). The NH₂ cluster of favipiravir binds to the RBD-ACE2 complex on Glutamate (B:940). RBD is a primary domain peptide in infectious pathogenesis. RBD is the active site of binding for Angiotensin-Converting Enzyme 2 (ACE2) receptors of humans. ACE2 is an enzyme located on the surface (membrane) of organ cells, such as the lungs, arteries, heart, kidneys, and intestines [53]. The SARS-CoV could infect the host cell through the ACE 2 receptor protein [54]. The SARS-CoV-2 protein spike has a strong binding affinity with human ACE2 [55]. The bonds with the ACE2 receptor was able to help the SARS-CoV-2 infected a host cell [56]. Therefore, the suspected Asp-Trp and Val-Tyr peptides can inhibit binding between the SARS-CoV-2 and the RBD spike. This inhibition allows delaying of viruses binding on the ACE2 receptors in the lungs and other tissues.

Figure 5 showed a binding visualization between the Asp-Trp and Val-Tyr peptides with deubiquitinase inhibitors blocks SARS virus replication (3E9S). The docking simulation results in the position of Asp-Trp, Val-Tyr, and favipiravir peptide bonds in the 3E9S protein, on the active side using hydrogen bonds. The amine group of Asp-Trp binds to protein 3E9S, in Tyrosine (A:265 and A:274). The carboxamide cluster of Asp-Trp binds to protein 3E9S on Glutamine (A:270). The Asp-Trp ester group binds to protein 3E9S in Threonine (A:302). The amine group of the Val-Tyr binds to protein 3E9S in Threonine (A:75). The carboxyl cluster of Val-Tyr binds to protein 3E9S on the Proline (A:60). Favipiravir's amine group binds with protein 3E9S on Glutamate (A:78) and Leucine (A:76). The SARS-CoV has two large polyproteins that have been coded in its genomic sequence, namely papain-like protease (PLpro) and the 3-chymotrypsin-like protease (3CLpro). Polyproteins in viruses plays important action in the virus maturation and infection [57]. These two polyproteins play a pivotal role in virus-mediated RNA replication, such as the SARS-CoV-2 (COVID-19) [58]. Both polyproteins are play key role in the virus life cycle and become a target of the SARS-CoV antiviral drug design [59].

Table 3 showed that Asp-Trp and Val-Tyr bioactive peptides from the tilapia viscera hydrolyzate extract meet drug-likeness rules and have LD50 (Prediction) which is safe for consumption. The bioactive peptide is a compound that has a health function for the human body. Bioactive peptides have unique amino acid structure and composition and have biological functions [60]. Bioactive

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peptides formed when encrypted peptides become active by acid hydrolysis, chemical alkali, proteolytic microorganisms, and enzymatic hydrolysis [61]. In this study, the viscera of tilapia hydrolyzed with the enzyme alcalase, and this hydrolysis process made extracts of tilapia viscera hydrolyzate contain bioactive peptides and have biological functions. Viscera is a fishery waste that could be used to obtain protein hydrolyzate, which is rich in bioactive peptides. Waste from agroindustry is a rich source of protein and can be an alternative in obtaining bioactivity compounds, especially protein hydrolyzate [62].

Previous study showed that a short-chain peptide (less than 30 strands of amino acids) have broad-spectrum antiviral properties [63]. These short-chain peptides may interact with virus and/or glycoprotein receptors through target cells to inhibit the bonding between receptors and viruses that can interfere with virus replication [64, 65]. Short-chain peptides can also disrupt the virus casing; therefore, it is impeded the virus from entering the target cell [66, 67]. Bioactive peptides are also reported to be antiviral in the H1N1 influenza virus, H5N1, and SARS-CoV [68]. Studies of the molecular docking peptide bioactive Asp-Trp and Val-Tyr from the tilapia viscera hydrolysate demonstrated its ability to bind to the viral receptor proteins' active site play a role in the replication, maturity, and inhibition of the SARS-CoV-2 virus (COVID 19) in the target protein.

Antiviral peptide tilapia hepcidin 1-5 modulate immune-related gene expressions against infectious pancreatic necrosis virus (IPNV) [69]. The antiviral peptide polyphemucine, tachyplesin, defensin-like isolated from crab and mussel possess antiviral activity [3]. Blood-like waste is also produced antiviral peptide [70]. This antiviral peptide potentially becomes an alternative in virus infections that invade the respiratory tract [71]. Also, the advantage of the antiviral peptide is synthetically produced [72, 73]. Therefore, an antiviral agent peptide-based is a promising therapeutic of the SARS-CoV-2 infection (COVID 19).

4. Conclusion

The bioactive peptides of Asp-Trp and Val-Tyr had better interaction with the SARS-CoV-2 protease (COVID 19) compared with chloroquine and favipiravir in the molecular docking study. In additions, bioactive peptides Asp-Trp and Val-Tyr exhibited better interaction with Spike-RBD, a receptor protein that directs the virus to attach to the ACE2 (the viral receptor target SARS-CoV-2). Besides, the bioactive peptides of Asp-Trp and Val-Tyr can bind to polyproteins instrumental in maturase and viral replication. Bioactive peptides of Asp-Trp and Val-Tyr could potentially be an antiviral peptide with targets stopping the infection and replication of the SARS-CoV-2 (COVID 19).

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9

PAGE 10

PAGE 11

PAGE 12

PAGE 13

PAGE 14

PAGE 15

PAGE 16