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Research Article

Study *In Silico* Pigment Derivative Compounds *Monascus sp*. As Anticorona Virus Candidates

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Abstract

Background: Corona Virus is biggest family of viruses with causes of illness ranging from mild to severe symptoms. *Monascus* sp. is used to ferment which has the potential as a Nutraceutical. Studies on *Monascus* sp. developing rapidly, including the discovery of new pigments, namely 57 derivatives of the pigment *Monascus* sp. Codes 5LHD and 6VW1 were used as anticoronavirus receptors.

Material and Methods: Ols and SwissDock and then validated by performing Molecular Dynamic. The final conformational results were then visualized using the Biovia Discovery studio, analyzed the effectiveness of the docking program, pharmacokinetics, toxicity, and dynamic programming using the Ramachandran plot.

Results: analysis showed that the compounds derived from *Monascus* sp. On average it has a small binding affinity value, but the Monankarin E compound has a so good binding affinity value (5LHD: -8.7).

Conclusion: Monankarin E from the pigment derivative *Monascus* sp. can provide good potential to use as a candidate for the anticorona virus.

Keywords: Pigment *Monascus sp.*; Anticorona Virus; *in Silico*

Introduction

At the beginning of 2020, the world was surprised by the emergence of a serious disease whose specific source was unknown. The World Health Organization (WHO) received obtained the genetic code, namely Coronavirus [1]. Coronavirus (CoV) is great families of virus that causes a disease ranging from mild to severe symptoms. There are at least two types of Coronavirus such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV) [2]. Indonesia has reached 8,340 people who get infected by this Coronavirus since the disaster emergency status was implemented on February 29, 2020 [3].

Monascus sp is yeast used to ferment white rice in order to produce red rice (Red Yeast Rice) which has potential as a Nutraceutical. Studies on *Monascus sp*. are rapidly develop. There were findings of new pigments which come from the main pigments, namely red, orange and yellow. From the six major pigments, fifty-seven derivatives has been founded so far [4]. There are fifty-seven compounds derived from the pigment of *Monascus sp*. which is not known yet if it has activity against the anti-coronavirus (COVID-19).

Materials and Methods

Instruments

The instruments used in this research were in the form of hardware and software computer, the device was a personal computer with Intel® Celeron® N4000 CPU @ 1.10Hz (2 CPUs) 4.96 GB RAM specifications with Windows 10 Professional operating system. The used software were chemBraw 3D, MarvinSketch, Autodock,

Molegro Molecul Viewer, Discovery Studio, Toxtree, MOE and other online server-based helper programs such as PreADMET, PDB.

Substances

The substantial used in this study were anti-coronavirus receptors that have been formed and identified, the codes were 5LHD and 6VWI which were downloaded from the Protein Data Bank (PDB) and fifty seven pigment-derived compounds from *Monascus sp*.

Ligand preparation

Ligands were drawn using ChemDraw software, then it was copied using the MarvinSketch software and next the geometric and

No	Compound Name	Chemical Formula	SMILES structure
Yellow			
1	Xantomonascin A	$C_{21}H_{22}O_7$	CCCCCC(=O)C1=C2c3oc(c(c3C[C@@]([C@]2(OC1=O)C)(O)/C=C/C)C=O)O
2	Xantomonascin B	$C_{24}H_{30}O_6$	CCCCCCCC(=O)C1=C(O)O[C@]2(C1=C1OC(=O)C(=C1C[C@@]2(O)/C=C/C)C=O)C
3	Yellow II	$C_{22}H_{28}O_5$	CCCCCCCC(=O)C1=C(O)OC2(C1=CC1=C/C(=C/C)/OCC1C2=O)C
4	Monankarin A-B	$C_{20}H_{22}O_6$	C[C@@H]1CC(=O)C=C(O1)c1cc2c(oc1=O)cc(c(c2[C@@H]([C@H](O)C)C)C)O
5	Monankarin C-D	$C_{21}H_{24}O_6$	CC1CC(=O)C=C(O1)c1cc2c([C@H]([C@H](O)C)C)c(C)c(c(c2oc1=O)C)O
6	Monankarin E	$C_{19}H_{20}O_6$	CC(Cc1cc(O)c(c2c1cc(C1=CC(=O)CC(O1)C)c(=O)o2)C)O
7	Monankarin F	$C_{21}H_{24}O_5$	CC1CC(=O)C=C(O1)c1cc2c(CC(O)C)c(C)c(c(c2oc1=O)C)O
8	Monascusone A	$C_{31}H_{18}O_5$	C[C@@H](CC1=CC2=C(CO1)C(=O)[C@]([C@H](C2)O)(C)O)O
9	Monascusone B	$C_{17}H_{18}O_5$	C/C=C/C1=CC2=C(CO1)C(=O)[C@]1([C@H](C2)[C@@H](C(=O)C)C(=O)O1)C
10	FK 17-P2B2	$C_{13}H_{16}O_4$	C/C=C/C1=CC2=C(CO1)C(=O)[C@]([C@H](C2)O)(C)O
11	Y3	$C_{21}H_{36}O_8S$	CC(CC(C(CC(=O)O)(O)C)(c1c(OC(=S)CC(O)C)cc(c(c1O)C)O)O)C
12	Monapurones A	$C_{20}H_{26}O_4$	CCCCCC(=O)C[C@@H]1C2=COC(=CC2=CC(=O)[C@]1(C)O)/C=C/C
13	Monapurones B	$C_{21}H_{28}O_4$	CCCCC[C@@]1(OC)C[C@H]2[C@](O1)(C)C(=O)C=C1C2=COC(=C1)/C=C/C
14	Monapurones C	$C_{21}H_{28}O_4$	CCCCC[C@]1(OC)C[C@H]2[C@](O1)(C)C(=O)C=C1C2=COC(=C1)/C=C/C
15	Monaphilol A	$C_{22}H_{32}O_4$	CCCCCCCC(=O)C[C@H]1CC2=C(C(=O)[C@]1(C)O)COC(=C2)/C=C/C
16	Monaphilol B	$C_{20}H_{28}O_4$	CCCCCC(=O)C[C@H]1CC2=C(C(=O)[C@]1(C)O)COC(=C2)/C=C/C
17	Monaphilol C	$C_{20}H_{32}O_4$	CCCCCC(=O)C[C@@H]1CC(=C(C(=O)[C@]1(C)O)C)CC(=O)CCC
18	Monashexenone	$C_{19}H_{28}O_4$	CCCCCC(CC1CC(CC(C=CC)=O)=C(C)C(C1O)=O)=O
19	Rubropuctin	$C_{22}H_{30}O_4$	CCCCCCCC(=O)CC1C=C2C=C(/C=C/C)OC=C2C(=O)C1(C)O
20	Monarubri	$C_{20}H_{26}O_4$	CCCCCC(=O)C1=C2C=C3C=C(/C=C/C)OC=C3C(=O)C2(OC1=O)C
21	Purpureusone	$C_{23}H_{34}O_5$	CCCCCCCC(=O)[C@H]1C(=O)O[C@@]2(C1CC(=C(C2=O)C)CC(=O)CCC)C
22	Monascuspiloin	$C_{21}H_{28}O_5$	[H][C@@]12CC3C=C(C=CC)OCC=3C([C@]2(C)OC([C@@H]1C(CCCCC)O)=O)=O
Red			
23	N-glucosyl rubropuctamine	$C_{30}H_{39}NO_9$	CCCCCC(=O)C1=C2C=c3cc(/C=C/C)n(cc3C(=O)[C@@]2(OC1=O)C)[C@H]1OC(CO)[C@@H]([C@H](C1O)O)O

24	N-glucosyl monascurobramine	$C_{32}H_{43}NO_9$	CCCCCCCC(=O)C1=C2C=c3cc(/C=C/C)n(cc3C(=O)[C@@]2(OC1=O)C)[C@H]1OC(CO)[C@@H]([C@H](C1O)O)O
25	N-glutaryl monasco-rubramine	$C_{28}H_{33}NO_8$	CCCCCCCC(=O)C1=C2C=c3cc(/C=C/C)n(cc3C(=O)C2(OC1=O)C)C(C(=O)O)CCC(=O)O
26	N-glutaryl rubropuctamine	$C_{30}H_{39}NO_9$	CCCCCC(=O)C1=C2C=c3cc(/C=C/C)n(cc3C(=O)C2(OC1=O)C)C(C(=O)O)CCC(=O)O
27	Red Derivat 1	$C_{26}H_{31}NO_6$	CCCCCCCC(=O)C1=C2C=c3cc(/C=C/C)n(cc3C(=O)[C@@]2(OC1=O)C)[C@H](C(=O)O)C
28	Red Derivat 2	$C_{24}H_{27}NO_6$	CCCCCC(=O)C1=C2C=c3cc(/C=C/C)n(cc3C(=O)[C@@]2(OC1=O)C)[C@H](C(=O)O)C
29	Red Derivat 3	$C_{27}H_{31}NO_8$	CCCCCCCC(=O)C1=C2C=c3cc(/C=C/C)n(cc3C(=O)[C@@]2(OC1=O)C)[C@H](C(=O)O)CC(=O)O
30	Red Derivat 4	$C_{25}H_{27}NO_8$	CCCCCC(=O)C1=C2C=c3cc(/C=C/C)n(cc3C(=O)[C@@]2(OC1=O)C)[C@H](C(=O)O)CC(=O)OC
31	Red Derivat 5	$C_{26}H_{31}NO_6$	CCCCCCCC(=O)C1=C2C=c3cc(/C=C/C)n(cc3C(=O)[C@@]2(OC1=O)C)[C@@H](C(=O)O)C
32	Red Derivat 6	$C_{24}H_{27}NO_6$	CCCCCC(=O)C1=C2C=c3cc(/C=C/C)n(cc3C(=O)[C@@]2(OC1=O)C)[C@@H](C(=O)O)C
33	Red Derivat 7	$C_{27}H_{31}NO_8$	CCCCCCCC(=O)C1=C2C=c3cc(/C=C/C)n(cc3C(=O)[C@@]2(OC1=O)C)[C@@H](C(=O)O)CC(=CO)O
34	Red Derivat 8	$C_{25}H_{27}NO_8$	CCCCCC(=O)C1=C2C=c3cc(/C=C/C)n(cc3C(=O)[C@@]2(OC1=O)C)[C@@H](C(=O)O)CC(=O)O
35	Isolate Mps 4	$C_{26}H_{33}NO_5$	CCCCCCCC(=O)C1=C2CC3=C(C(=O)[C@@]2(OC1=O)C)CN(C(=C3)/C=C/C)CC(=O)O
36	Isolate Mps 3	$C_{22}H_{29}O_6$	CCCCCCCC(=O)C1=C2C=c3cc(/C=C/C)n(cc3C(=O)C2(OC1=O)C)CC(=O)O
37	Isolate Mps 2	$C_{25}H_{38}N_4O_6$	CCCCCCCC(=O)C1=C2C=c3cc(/C=C/C)n(cc3C(=O)C2(OC1=O)C)C(C(=O)O)CCCNC(=NN
38	Isolate Mps 1	$C_{23}H_{34}N_4O_6$	CCCCCC(=O)C1=C2C=c3cc(/C=C/C)n(cc3C(=O)C2(OC1=O)C)C(C(=O)O)CCCNC(=N)N
39	New Red Pigment	$C_{21}H_{29}O_5$	CCCCCC(C1C(=O)OC2(C1c1c[nH]c(cc1=CC2=O)CC(O)C)C)O
40	Compound R3	$C_{21}H_{26}O_6$	CCCCCC(=O)C1C(=O)OC2(C1C1=COC(=CC1=CC2=O)CC(O)C)C
41	Monascopyridine A	$C_{21}H_{25}NO_4$	CCCCCC(=O)[C@@H]1C(=O)O[C@]2([C@H]1Cc1cc(/C=C/C)ncc1C2=O)C
42	Monascopyridine B	$C_{23}H_{29}NO_4$	CCCCCCCC(=O)[C@@H]1C(=O)O[C@]2([C@H]1Cc1cc(/C=C/C)ncc1C2=O)C
43	Monascopyridine C	$C_{21}H_{27}NO_4$	CCCCCC(=O)C[C@@H]1Cc2cc(/C=C/C)ncc2C(=O)[C@@]1(C)O
44	Monascopyridine D	$C_{21}H_{29}NO_3$	CCCCCCCC(=O)C[C@@H]1Cc2cc(/C=C/C)ncc2C(=O)[C@@]1(C)O
45	Unamed	$C_{21}H_{29}NO_5$	C/C=C/C1=CC2=CC3=[O+]NOC3(C(C2CN1C(C(=O)O)CCCCN)O)C
46	PP-V	$C_{23}H_{25}NO_6$	CCCCCCCC(=O)C1=C2C=C3C=C(/C=C\C(=O)[O-])[NH2+]C=C3C(=O)C2(OC1=O)C

47	Glycyl-rubropuntatin	$C_{23}H_{27}NO_6$	CCCCCC(=O)C1=C2CC3=C(C(=O)[C@@]2(OC1=O)C)CN(C(=C3)/C=C/C)CC(=O)O
48	Red Shandong 1	$C_{18}H_{25}NO_3$	C=CCCCC(C1=CC2=C/C(=C/C=C)/NCC2C(C1O)O)O
49	Red Shandong 2	$C_{20}H_{29}NO_3$	C=CCCCCCC(C1=CC2=C/C(=C/C=C)/NCC2C(C1O)O)O
Blue			
50	Monasfluor A	$C_{22}H_{26}O_4$	CCCCCC(=O)C1C(=O)OC2(C1C1=COC(=CC1=CC2=O)/C=C/C)C
51	Monasfluor B	$C_{23}H_{28}O_5$	CCCCCCCC(=O)C1C(=O)OC2(C1C1=COC(=CC1=CC2=O)/C=C/C)C
Orange			
52	Monaphilo 1A	$C_{23}H_{28}O_5$	CCCCCCCC(=O)C1=C2C=C3C=C(/C=C/C)OC=C3[C@@H]([C@@]2(OC1=O)C)O
53	Monaphilo 1B	$C_{21}H_{24}O_5$	CCCCCC(=O)C1=C2C=C3C=C(/C=C/C)OC=C3[C@@H]([C@@]2(OC1=O)C)O
54	Monaphilo 1C	$C_{26}H_{32}O_6$	CCCCCCCC(=O)C1=C2C=C3C=C(/C=C/C)OC=C3[C@]([C@@]2(OC1=O)C)(O)CC(=O)C
55	Monaphilo 1D	$C_{24}H_{28}O_6$	CCCCCC(=O)C1=C2C=C3C=C(/C=C/C)OC=C3[C@]([C@@]2(OC1=O)C)(O)CC(=O)C
Colorles Oil			
56	Monascuskaodione A	$C_{21}H_{24}O_5$	CC1COC2C3C(C=O)C(=O)OC3(C)C(C=C2C=1)=O
57	Monascuskaodione B	$C_{23}H_{28}O_5$	CC1CC=C2C3C(C=O)C(=O)OC3(C)C(C=C2C=1)=O

Table 1: SMILES structure of *Monascus sp.*

protonation optimization were carried out at pH 7.4 then the file was saved in mol2 format [5].

Drug scan

Observations of drugs were tested on dye compounds of substances derived from *Monascus sp*. and taking into account the provisions of the rule of good medicine (Lipinski's rule of five) which molecular weight <500 g/mol, lipophilicity <5, hydrogen bond donor <5, hydrogen bond acceptor <10, and molate refractory around 40-130 and oral bioavailability of ligand [5].

PreADME

PreADME was accessed via preadmet.bmdrc.kr. The parameters used by PreADME were the values of $CaCo_2$, Human Intestinal Absorption (HIA), and Plasma Protein Binding (PPB).

Toxicity test

Toxicity test was conducted on derivative compounds of *Monascus sp*. pigment using the ToxTree software. The parameters seen in this toxicity test were the predictions of the Cramer Rules parameters, Kroes TTC decision tree and Benigni/Bossa rule base [6].

Receptor preparation

The anti-coronavirus receptor used was downloaded from the Protein Data Bank (PDB). A total of 2 receptors that has been downloaded was a receptor with 5LHD and 6VWI codes and then it optimized using Autodock software.

Docking method validation

Ligands that are said to be valid or not, must go through a process called docking validation. This docking validation aimed to assess which ligands are valid and can pass the docking process. The supporting software in this docking validation was the Autodock Tools where the parameter used was Root Mean Square Deviation (RMSD). The docking method is valid if the RMSD value is <2 Å [5].

Docking ligand test and result visualization

The derived compounds from *Monascus sp*. that has been optimized were docked to the protein whose natural ligands has been

removed using the Autodock Tools with the same docking procedure in validating procedure. The results of the analysis showed the bond conformation of the compound on proteins with bond strength and hydrogen bond values [7]. The visualization of interactions was the result from the docked receptor and ligand then it converted into the next .pdb form that will be analyzed using the Discovery Studio software by looking at the interactions in its 2D and 3D shapes.

Docking result analysis

The analysis of the results in the form of ligand conformation with the lowest energy was obtained based on the findings of the docking between ligand and receptor. The stronger the affinity between receptor and ligand, then the lower the binding affinity value, and vice versa the higher the binding affinity value, then the greater the affinity among receptors [4].

Molecular dynamics (MOE)

Molecular Dynamic (MD) ligands and proteins were optimized by Molecular Operating Environment (MOE) 2019.10 software. Geometry optimization and energy minimization of anti-coronavirus proteins were carried out using MOE software with the protein structure .pdb format were added to parameters such as hydrogen atom, partial determination, and gas phase. The addition of hydrogen atoms and protonation were carried out on proteins. Protein energy was minimized by the Merck Molecular Medan field 94x (MMFF94x). The protein was carried out in the born phase solvation with a constant charge and then it optimized with a Root Mean Square gradient (RMS) of 0.05 kcal/Åmol. The overall optimization file was obtained in .moe format [8].

In addition, the ligand energy was minimized using minimal energy with an RMS gradient of 0.0005 kkal/Åmol and the resulting file which was saved in .mdb format (Noviardi and Fachrurrazie, 2015). The MD was used a triangle matching by repeated energy readings for each position in the run of 100 times. The MD calculations were visible in the .mdb viewer output format. A number of ligand protein interaction parameters can be analyzed, including binding free energy (AG) and affinity (pKi). The chosen ligand protein complex was the smallest bond energy and the highest binding affinity [9].

Results and Discussion

Ligand Preparation

Ligand preparation was carried out on fifty-seven compounds derived from *Monascus* sp. by creating a 2-dimensional ligand structures using ChemDraw Professional 16.0 software. After that, it was copied using the MarvinSketch software. Then it was optimized for geometry and protonation at pH 7.4. Out of fifty-seven compounds derived from *Monascus* sp., samples of Compound R3 test ligands were taken as follows:

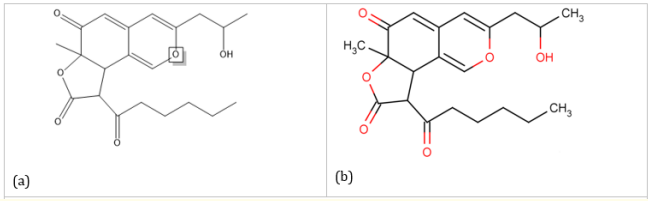

Figure 1: (a) Initial Compound R3 Ligand (b) Compound R3 Ligand after protonation.

Protonation at pH 7.4 was carried out until the pH matches the pH in the blood. Then a conformational search was carried out to obtain the lowest energy in order to obtain the most stable position of the molecule to interact with the active site of the receptor. Furthermore, the file is saved in .mrv and .mol2 formats [5]. The optimization of the structure also aimed to see the conformation of the molecule and see the low energy potential that has been regulated based on pH conditions in the human body [7].

Drug scan

The Drug scan was carried out to check the properties of ligand to be tested by considering the provisions of Lipinski's rule of five. This refers to the similarity of a compound with an oral drug [6]. These parameters can be seen from the help of the MarvinSketch software. The following are the results of the drug scan test:

Based on the results in table 2, drug scan for compounds derived from the pigment *Monascus* sp. which shows that not all met Lipinski's rule of five. There are 19 compounds *Monascus* sp. which does not met Lipinski's rule of five i.e. Y3, Purpureusone, N-glucosylrubropuctamine, N-glucosylmonascurobramine, N-glutaryl mo-

No	Compound Name	Drug Scan				
		Molecular Weight	Hydrogen Bond Donor	Hydrogen Bond Acceptor	Log P	Refractory Molar
		<500 g/mol	<5	<10	<5	40-130
		Yellow				
1	Xantomonascin A	388.4111	2	8	4.00	102.20
2	Xantomonascin B	414.4914	2	8	3.76	126.81
3	Yellow II	372.4547	1	7	4.31	116.32
4	Monankarin A-B	372.4547	1	7	4.31	116.32
5	Monankarin C-D	372.4117	2	7	2.90	103.14
6	Monankarin E	358.3851	2	7	2.53	98.67
7	Monankarin F	356.4123	2	6	2.99	103.21
8	Monascusone A	254.2790	3	6	-0.99	67.08
9	Monascusone B	302.3218	0	7	1.64	82.07
10	FK 17-P2B2	236.2637	2	5	0.35	66.34
11	**Y3**	**448.571**	**6**	**8**	**0.34**	**115.88**
12	Monapurones A	330.4180	1	6	2.98	97.87
13	Monapurones B	344.4446	0	5	3.93	101.83
14	Monapurones C	344.4446	0	3	3.93	101.83
15	Monaphilol A	374.5137	1	6	4.61	111.50
16	Monaphilol B	332.4339	1	6	3.27	97.70
17	Monaphilol C	336.4657	1	7	4.14	95.95
18	Monashexenone	320.4232	1	7	3.70	92.33
19	Rubropuctin	358.4712	1	6	4.02	107.15
20	Monarubri	330.4180	1	6	3.13	97.95
21	**Purpureusone**	**390.5131**	**0**	**8**	**5.43**	**107.95**
22	Monascuspiloin	360.4440	1	6	3.11	101.32
		Red				
23	**N-glucosyl rubropuctamine**	**557.640**	**4**	**17**	**2.65**	**149.92**
24	**N-glucosyl monascurobramine**	**585.694**	**4**	**17**	**3.54**	**159.12**
25	**N-glutaryl monascorubramine**	**511.571**	**2**	**15**	**4.30**	**138.82**
26	**N-glutaryl rubropuctamine**	**483.517**	**2**	**15**	**3.41**	**129.62**
27	**Red Derivat 1**	**453.535**	**1**	**11**	**4.65**	**128.03**
28	**Red Derivat 2**	**425.481**	**1**	**11**	**3.76**	**118.83**
29	**Red Derivat 3**	**497.544**	**2**	**15**	**4.01**	**134.07**
30	**Red Derivat 4**	**469.490**	**2**	**15**	**3.12**	**124.87**
31	**Red Derivat 5**	**453.535**	**1**	**11**	**4.65**	**128.03**
32	**Red Derivat 6**	**425.481**	**1**	**11**	**3.76**	**118.83**

33	**Red Derivat 7**	**497.544**	**2**	**15**	**4.01**	**134.07**
34	**Red Derivat 8**	**469.490**	**2**	**15**	**3.12**	**124.87**
35	Isolate Mps 4	439.552	1	9	4.32	126.87
36	**Isolate Mps 3**	**439.508**	**1**	**11**	**4.08**	**123.54**
37	**Isolate Mps 2**	**538.645**	**5**	**14**	**3.74**	**161.46**
38	**Isolate Mps 1**	**510.591**	**5**	**14**	**2.85**	**152.26**
39	New Red Pigment	375.465	3	9	1.16	103.91
40	Compound R3	374.433	1	10	2.05	101.41
41	Monascopyridine A	355.434	0	7	4.23	98.81
42	**Monascopyridine B**	**383.488**	**0**	**7**	**5.12**	**108.01**
43	Monascopyridine C	357.450	1	9	3.90	99.88
44	Monascopyridine D	343.467	1	7	4.61	100.56
45	Unamed	375.465	3	9	1.16	103.91
46	PP-V	412.461	3	10	3.26	125.22
47	**Glycyl-rubropuntatin**	**413.470**	**1**	**11**	**3.33**	**114.09**
48	Red Shandong 1	303.402	4	7	0,54	91.77
49	Red Shandong 2	331.456	4	7	1.43	100.98
		Blue				
50	Monasfluor A	354.4394	0	5	3.98	104.30
51	Monasfluor B	384.4654	0	7	4.27	109.87
		Orange				
52	Monaphilo 1A	384.4654	1	6	3.62	111.10
53	Monaphilo 1B	356.4123	1	6	2.73	101.89
54	Monaphilo 1C	440.5287	1	8	3.59	125.32
55	Monaphilo 1D	412.4755	1	8	2.70	116.12
		Colorles Oil				
56	Monascuskaodione A	356.418	0	8	3.36	100.67
57	Monascuskaodione B	384.472	0	8	4.27	109.87

Table 2: Drug scan results for compounds derived from *Monascus sp.*

***Bold Marked**: compounds that do not meet the requirements.

nascorubramine, N-glutaryl rubropuctamine, Red Derivat 1, Red Derivat 2, Red Derivat 3, Red Derivat 4, Red Derivat 5, Red Derivat 6, Red Derivat 7, Red Derivat 8, Isolate Mps 3, Isolate Mps 2, Isolate Mps 1, Monascopyridine B, Glycyl-rubropuntatin. While the compounds derived from *Monascus* sp. which met the Lipinski's rule of i.e Xantomonascin A, Xantomonascin B, Yellow II, Monankarin A-B, Monankarin C-D, Monankarin E, Monankarin F, *Monascus*one A, *Monascus*one B, FK 17-P2B2, Y3, Monapurones A, Monapurones B, Monapurones C, Monaphilol A, Monaphilol B, Monaphilol C, Monashexenone, Rubropuctin, Monarubri, *Monascus*piloin, Isolate Mps 4, New Red Pigment, Compound R3, Monascopyridine A, Monascopyridine C, Monascopyridine D, Unamed, PP-V, Red Shandong 1, Red Shandong 2, Monasfluor A, Monasfluor B, Monaphilo 1A, Monaphilo 1B, Monaphilo 1C, Monaphilo 1D, *Monascus*kaodione A, *Monascus*kaodione B.

The molecular weight value was related to the drug distribution process; so that a drug with a molecular weight value of less than

500 g/mol will easily penetrate cell membranes compared to a ligand with a molecular weight of more than 500 g/mol because it will have a large molecular size so it is quite difficult to penetrate biological membranes [11].

Lipophilicity/Log P is the main physicochemical determination that affects the bioavailability, permeability and toxicity of a drug. The Log P value was related to the polarity of the ligand in the solvents of fats, oils, and non-polar solvents. Ligands with a Log P value < 5 will easily penetrate the lipid bilayer layer on the cell membrane and are widely distributed in growth. This causes the sensitivity of the ligand binding to the target molecule to decrease and the ligand toxicity to increase. If the value was > 5 then a compound will stay in the lipid bilayer longer and be distributed more widely in the body so that the selectivity of binding to the target enzyme was reduced and causes higher toxicity [12].

The number of hydrogen donors and acceptors affected the hydrogen bonds that occur. Hydrogen bond was the bond of H atoms with other electronegative atoms such as O, N, and F. Hydrogen bonds indicated the polarity of a compound where the more hydrogen bonds, the more polar the compound because it bond to many oxygen molecules from water in the liquid [13].

Refractory molar is a value for the total polarizability of the drug molecule which was highly dependent on temperature, refractive index and pressure. Polarisability is the ease with which a molecule will form an instantaneous dipole or to induce a molecule [6].

PreADME

The ADME test was carried out using an online-based server, namely PreADMET which only refers to the absorption and distribution process, in the form of the value of $CaCo_2$, Human Intestinal Absorption (HIA), and Plasma Protein Binding (PPB). Here are the results of PreADMET.

No	Compound Name	$Caco_2$ (nm/sec)	HIA (Human Intestinal Absorption) %	PPB (Protein Plasma Binding) %
Kuning				
1	**Xantomonascin A**	**19.6124 Medium**	**88.865206 Good**	**96.842726 Strongly Bonded**
2	**Xantomonascin B**	**26.5245 Medium**	**94.538788 Good**	**94.764093 Strongly Bonded**
3	**Yellow II**	**34.2219 Medium**	**96.423561 Medium**	**91.738989 Strongly Bonded**
4	Monankarin A-B	21.4435 Medium	93.56731 Good	85.58307 Weakly Bonded
5	Monankarin C-D	21.9971 Medium	93.909198 Good	87.093425 Weakly Bonded
6	Monankarin E	21.4031 Medium	93.567883 Good	84.456494 Weakly Bonded
7	Monankarin F	35.5122 Medium	93.789307 Good	88.543275 Weakly Bonded

8	Monascusone A	19.3778 Medium	78.683369 Good	34.939799 Weakly Bonded
9	Monascusone B	22.9891 Medium	97.536574 Good	61.438550 Weakly Bonded
10	**FK 17-P2B2**	**0.993** **Rendah**	**90.43201** **Good**	**56.07652** **Weakly Bonded**
11	Monapurones A	26.9554 Medium	95.760530 Good	86.135746 Weakly Bonded
12	Monapurones B	44.272 Medium	97.697949 Good	88.300451 Weakly Bonded
13	Monapurones C	44.272 Medium	97.697949 Good	88.300451 Weakly Bonded
14	**Monaphilol A**	**48.8546** **Medium**	**96.052979** **Good**	**94.089855** **Strongly Bonded**
15	**Monaphilol B**	**40.8229** **Medium**	**96.054536** **Good**	**90.112573** **Strongly Bonded**
16	Monaphilol C	26.9554 Medium	95.760530 Good	86.135746 Weakly Bonded
17	Monashexenone	22.609 Medium	95.857284 Good	88.158433 Weakly Bonded
18	**Rubropuctin**	**46.2928** **Medium**	**96.050080** **Good**	**95.896405** **Strongly Bonded**
19	**Monarubri**	**40.5147** **Medium**	**96.071613** **Good**	**92.263384** **Strongly Bonded**
20	**Monascuspiloin**	**30.4892** **Medium**	**96.468903** **Good**	**90.306522** **Strongly Bonded**
Merah				
21	**Isolate Mps 4**	**25.6923** **Medium**	**99.303546** **Good**	**92.314035** **Strongly Bonded**

22	New Red Pigment	17.9896 Medium	89.666473 Good	66.572743 Weakly Bonded
23	Compound R3	17.4163 Medium	95.677133 Good	73.231309 Weakly Bonded
24	**Monascopyridine A**	**26.367** **Medium**	**98.750840** **Good**	**91.953695** **Strongly Bonded**
25	Monascopyridine C	22.7729 Medium	96.648798 Good	89.685299 Weakly Bonded
26	**Monascopyridine D**	**22.9611** **Medium**	**96.270412** **Good**	**97.268350** **Strongly Bonded**
27	Unamed	17.9896 Medium	89.666473 Good	66.572743 Weakly Bonded
28	PP-V	4.01366 Medium	92.923736 Good	86.114618 Weakly Bonded
29	Red Shandong 1	13.6843 Medium	85.719545 Good	71.398196 Weakly Bonded
30	Red Shandong 2	14.2523 Medium	87.122330 Good	87.278357 Weakly Bonded
Biru				
31	**Monasfluor A**	**49.808** **Medium**	**97.649968** **Good**	**92.794086** **Strongly Bonded**
32	**Monasfluor B**	**36.0846** **Medium**	**98.771155** **Good**	**92.381422** **Strongly Bonded**
Orange				
33	**Monaphilo 1A**	**36.7103** **Medium**	**96.501044** **Good**	**95.427557** **Strongly Bonded**
34	**Monaphilo 1B**	**29.408** **Medium**	**96.568439** **Good**	**91.926288** **Strongly Bonded**
35	Monaphilo 1C	34.038 Medium	97.366571 Good	89.549401 Weakly Bonded

36	Monaphilo 1D	27.7997 Medium	97.311031 Good	83.639250 Weakly Bonded
Colorles Oil				
37	Monascuskaodione A	28.3725 Medium	98.770329 Good	88.897997 Weakly Bonded
38	**Monascuskaodione B**	**36.0846** **Medium**	**98.771155** **Good**	**92.381422** **Strongly Bonded**

Table 3: PreADME results for *Monascus sp.*

*Bold Marked: Compounds that do not meet the requirements.

$CaCo_2$: Low <4; Medium 4-70; High >70

HIA: Low 0-20%; Medium 20-70%; Good 70-100%

PPB: Weakly Bonded <90%; Strongly Bonded >90%.

Table 3 is the result of PreADME using the PreADMET program for fifty-seven compounds derived from *Monascus sp*. which had previously been eliminated in the drug scan test. Based on the results of the CaCo2 value, a moderate value was obtained in the range of less than 4, namely only the FK 17-P2B2 (0.993) compound which had low permeability. Because a good value based on the absorption process in the human intestine is 4-70.

Prediction of drug absorption was carried out based on the ability of a drug to be absorbed in the intestinal wall or known as HIA (Human Intestinal Absorption) prediction. This was conducted because when the drug is given orally, then the drug must be well absorbed in the intestinal wall, so that it can pass through the blood vessels, but if the absorption ability is low, the drug will not be able to reach its target receptor. Therefore, the HIA test is important to do [14].

Then for the value of Plasma Binding Protein (PPB) Xantomonascin A, Xantomonascin B, Yellow II, Monaphilol A, Monaphilol B, Rubropuctin, Monarubri, *Monascus*piloin, Isolate Mps 4, Monascopyridine A, Monascopyridine D, *Monascus*kaodione B, Monasfluor A, Monasfluor B, Monaphilo 1A, Monaphilo 1B compounds had the high value that is > 90% indicated a strong bond with plasma protein binding in the body. While the low bond value <90% is Monankarin A-B, Monankarin C-D, Monankarin E, Monankarin F, *Monascus*one A, *Monascus*one B, FK 17-P2B2, Y3, Monapurones A, Monapurones B, Monapurones C, Monaphilol C, Monashexenone, New Red Pigment, Compound R3, Monascopyridine C, Unamed, PP-V, Red Shandong 1, Red Shandong 2, Monaphilo 1C, Monaphilo 1D, *Monascus*kaodione A compounds which showed a weak bond with the weak binding of plasma proteins in the body.

Toxicity test

One of the softwares that can be used to perform toxicity tests on humans is Toxtre. Toxtre is an application that is able to estimate the toxicity of a molecule. This toxicity test was carried out on fifty-seven compounds derived from the pigment *Monascus* sp. which previously had been eliminated in the ADME test, so that the compounds obtained were twenty-two compounds derived from *Monascus* sp. The following are the results of the toxicity test using the Toxtre software.

Toxicity parameters used were Cramer Rules to see the level of toxicity seen from its functional group, Kroes TTC decision tree to estimate the exposure thresholds for drug compounds in humans, and Benigni/Bossa rulebase to determine whether these compounds can cause carcinogenicity and mutagenicity [6].

No	Compound Name	Parameter		
		Cramer Rules	Kroes TTC decision tree	Benigni/Bossa rule-base
		Yellow		
1	Monankarin A-B	3	8	11
2	Monankarin C-D	3	8	11
3	Monankarin E	3	8	11
4	Monankarin F	3	8	11
5	Monascusone A	3	8	11
6	Monascusone B	3	8	11
7	Monapurones A	3	8	11
8	Monapurones B	3	8	11
9	Monapurones C	3	8	11
10	Monaphilol C	3	8	11
11	Monashexenone	2	8	11
		Red		
12	New Red Pigment	3	8	11
13	Compound R3	3	8	11
14	Monascopyridine C	3	8	11
15	Unamed	3	8	11
16	PP-V	3	8	11
17	Red Shandong 1	3	9	11
18	Red Shandong 2	3	9	11
		Orange		
19	Monaphilo 1C	3	8	11
20	Monaphilo 1D	3	8	11
		ColorlesOil		
21	Monascuskaodione A	3	8	11

Table 4: Toxicity test results using Toxtre.

*Cramer Rules: 2: Medium (Kelas II), 3: High (Kelas III).

Kroes TTC decision tree: 8: Risk ignored, 9: Substances are not expected to be a safety issue.

Benigni/Bossa rulebase: 10: Negative for nongenotoxic carcinogenicity.

Cramer Rules were used to remove non-carcinogenic chemicals and to determine TTC levels. Cramer Rules had original questions consisting of 33 questions or Yes or No rules. The answers to each question lead to other questions until the final Cramer Rules classification for the chemical of interest is established. Cramer Rules classify materials into one of three classes (Class I-Low, Class II-Intermediate, and Class III-High). Meanwhile, those with moderate toxicity Class II was Monashexenone compound, which means substance that have a less dangerous structure than Class I substances, but does not contain structural features that indicate toxicity as substances in Class III [15].

Based on the Cramer Rules Class III parameters, Monankarin AB, Monankarin CD, Monankarin E, Monankarin F, *Monascus*one A, *Monascus*one B, FK 17-P2B2, Monapurones A, Monapurones B, Monapurones C, Monaphilol C, New Red Pigment, Compound R3, Monascopyridine C, Unamed, PP-V, Red Shandong 1, Red Shandong 2, Monaphilo 1C, Monaphilo 1D, *Monascus*kaodione A componds has high toxicity (Class III). It means that high concentrations of these compounds do not guarantee their safety in use. It was stated that Class III has a substance from a chemical structure which in terms of safety has a weak initial effect [16].

Kroes TTC decision tree Monankarin A-B, Monankarin C-D, Monankarin E, Monankarin F, *Monascus*one A, *Monascus*one B, FK 17-P2B2, Monapurones A, Monapurones B, Monapurones C, Monaphilol C, Monashexenone, New Red Pigment, Compound R3, Monascopyridine C, Unamed, PP-V, Monaphilo 1C, Monaphilo 1D, *Monascus*kaodione compounds, the exposure threshold is not more than 0.15 g/day. It is based on the analysis of dose response data of carcinogenic compounds. This threshold gave an 86-97% chance that some risks may be reduced by 0.15 µg/day, under this compound became a genotoxic carcinogen. This chemical substance is not freely recommended for fixed food supplies [17]. While Red Shandong 1 and Red Shandong 2 has a substance threshold that is not expected to be a safety issue.

Meanwhile for Benigni/Bossa rulebase parameters, no compound has a structure that contributed as a caryogenic genotoxic drug. Then the compound Monankarin A-B, Monankarin C-D, Monankarin E, Monankarin F, *Monascus*one A, *Monascus*one B, FK 17-P2B2, Monapurones A, Monapurones B, Monapurones C, Monaphilol C, Monashexenone, New Red Pigment, Compound R3, Monascopyridine C, Unamed, PP-V, Red Shandong 1, Red Shandong 2, Monaphilo 1C, Monaphilo 1D, *Monascus*kaodione A negatively contributed to non-toxic carcinogenicity [18].

Receptor preparation

The receptor preparation in this study was by downloading the anticoronavirus receptor on the Protein Data Bank. There are 2 receptors, which are coded: 5LHD and 6VW1 from some selected receptors, 2 receptors has good RMSD values. Then the receptor was downloaded in .pdb format.

Validation of docking method

Validation of this docking method was conducted by redocking natural ligands on proteins that had been previously downloaded from the Protein Data Bank (PDB). This validation aimed to see whether the method used is valid or not. The parameter seen for this validation evaluation was the RMSD (Root Mean Square Deviation) value. RMSD is a value which obtained from the result of a measurement of two poses by comparing the atomic position between the experimental structure and the structure docked in the protein [19]. The docking method is valid if the RMSD value is < 2. The results of the docking validation can be seen in table 5 below.

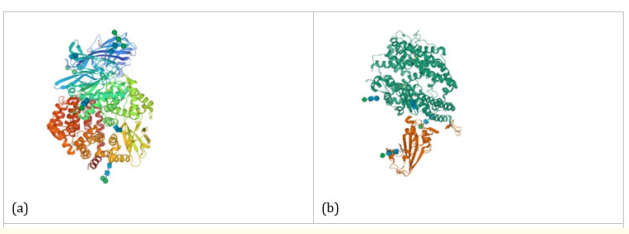

Figure 2: (a) 5LHD protein (b) 6VW1 protein.

Receptor	GRID BOX			RMSD
	X	Y	Z	
5LHD	-36.161	-31.933	25.394	1.24
6VW1	114.866	25.439	145.547	1.66

Table 5: Docking validation results.

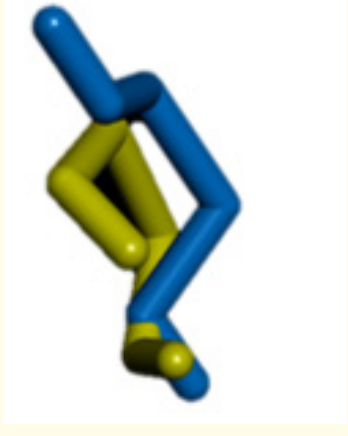

Figure 3: Overlap (natural ligand: blue, copy ligand: greenish yellow) with Code 5LHD.

Figure 4: Overlap (natural ligand: red, copy ligand: greenish yellow) with Code 6VW1.

Based on the validation results, the RMSD value for the anticorona virus receptor 5LHD code was 1.24, while the value for the receptor 6VW1 code was 1.66, the value is stated <2. The smaller the RMSD value indicates that the predicted ligand pose was getting better because it is closer to the natural ligand. The grid box 5LHD code is X= -36.161, Y= -31.933, Z= 25.394 while the 6VW1 code is X= -114.866, Y= 25,439, Z= 145.547. then from the validation results above, receptors with 5LHD and 6VW1 codes meets the validation criteria for the docking method so that they can be used on the test ligand.

Docking of ligand test and visualization the results

The results of Docking between the ligand and the target protein will produce various conformations of the compound that will be used. Bond energy is one of the docking results that must be considered (binding affinity). Bond affinity (ΔG) with a unit value of kcal/mol can be used to determine the best conformation. The binding energy value will describe the strength of the bond that occured between the ligand and the target protein [20]. The results of each conformation between the ligands to the target protein is in the table 6.

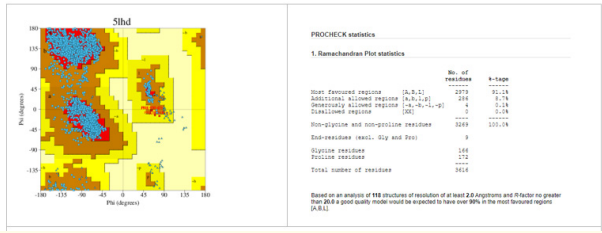

Figure 5: Ramachandran Plot visualization results and procheck statistics.

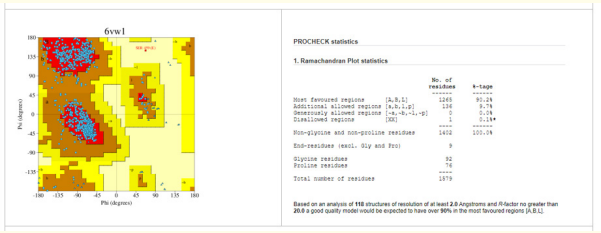

Figure 6: Ramachandran Plot visualization results and procheck statistics.

No	Nama Senyawa	Binding Affinity Kkal/mol	
		5LHD	6VW1
1	Ligan Alami	-3.4	-3.2
Yellow			
1	Monankarin A-B	-8.6	-6.7
2	Monankarin C-D	-8.7	-6.2
3	Monankarin E	-8.7	-7.3
4	Monankarin F	-8.3	-6.0
5	Monascusone A	-6.8	-6.0
6	Monascusone B	-7.7	-6.4
7	Monapurones A	-7.1	-6.6
8	Monapurones B	-7.0	-6.7
9	Monapurones C	-7.1	-7.3
10	Monaphilol C	-6.2	-5.4
11	Monashexenone	-6.8	-6.3
Red			
12	New Red Pigment	-7.6	-6.0
13	Compound R3	-6.9	-6.5
14	Monascopyridine C	-7.9	-7.2

15	Unamed	-8.0	-7.1
16	PP-V	-7.9	-7.4
17	Red Shandong 1	-7.0	-5.8
18	Red Shandong 2	-6.6	-6.5
Orange			
19	Monaphilo 1C	-7.5	-7.3
20	Monaphilo 1D	-7.5	-5.7
Colorles Oil			
21	Monascuskaodione A	-7.8	-5.9

Table 6: Results of Interaction of Ligands with Test Target Proteins.

The results in table 6 showed that all natural ligand, comparison ligand and test ligand has the ability to bind with target proteins. According to the analysis above, almost all natural ligands and test ligands has a small binding affinity value. The results of binding affinity 21 compounds derived from the pigment *Monascus* sp. The 5 best compounds were taken from those with the best binding affinity, 5LHD code that are Monankarin AB (-8.6), Monankarin CD (-8.7), Monankarin E (-8.7), Monankarin F (-8.3) and Unamed (-8.0), and 6VW1 code that are Monankarin E (-7.3), Monapurones C (-7.3), Monascopyridine C (-7.2), PP-V (-7.4) and Monaphilol 1C (-7.3). This shows that the test compound derived from the pigment *Monascus* sp can inhibit the target protein well and stable. After the docking process for the test compound was completed, the next step was to visualize the docking results in 2D and 3D forms.

The visualization results is the result of the test compound tethering with the target protein which aimed to see the interaction between the ligand and amino acid residues on the receptor by visualization. The interactions that can be observed in this process were including hydrogen bonds and hydrophobic bonds [21]. The compounds visualized were compounds derived from the pigment *Monascus* sp, which has a good value at the time of testing and has the best binding affinity value. This visualization was conducted by Discovery Studio software version 16.1. The following is a visualization of the analysis of the docking results with the 5LHD protein code based on 2D and 3D using the Discovery Studio software.

Analysis of docking results

The conformation with the smallest energy obtained from the results of docking between ligands and receptors. Binding affinity is a measure of a drug's ability to bind with receptor [22]. By the

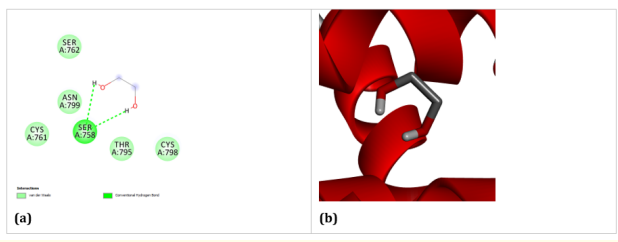

Figure 7: (a) The results of docking natural ligand compounds with 2D protein and (b) 3D with 5LHD protein.

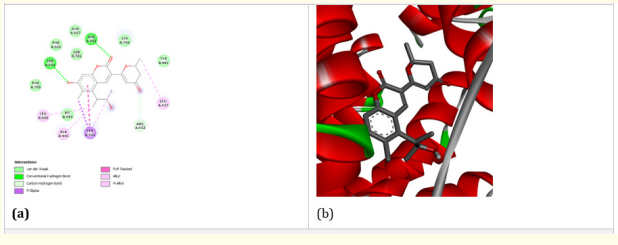

Figure 8: (a) The results of 2D docking of Monankarin A-B compounds and (b) 3D with 5LHD protein.

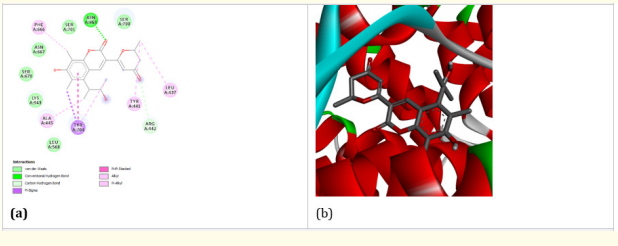

Figure 9: (a) The results of 2D docking of Monankarin C-D compounds and (b) 3D with 5LHD protein.

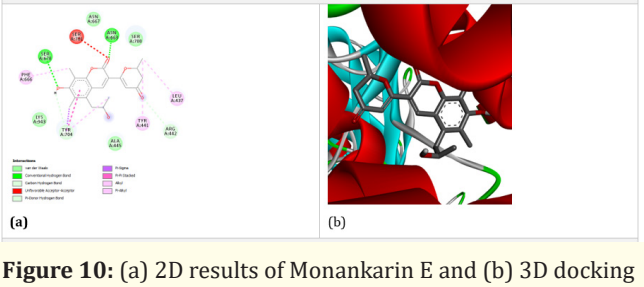

Figure 10: (a) 2D results of Monankarin E and (b) 3D docking with 5LHD. Protein.

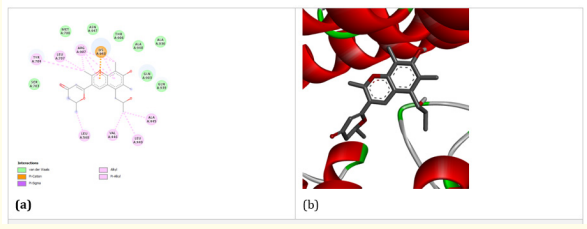

Figure 11: (a) 2D results of Monankarin F and (b) 3D docking with 5LHD protein.

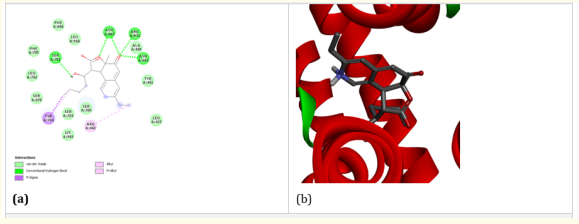

Figure 12: (a) Results of 2D docking of Unamed compounds and (b) 3D with 5LHD protein.

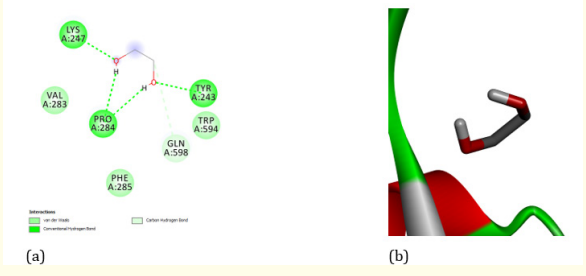

Figure 13: (a) 2D results of docking natural ligand compounds and (b) 3D with 6VW1 protein.

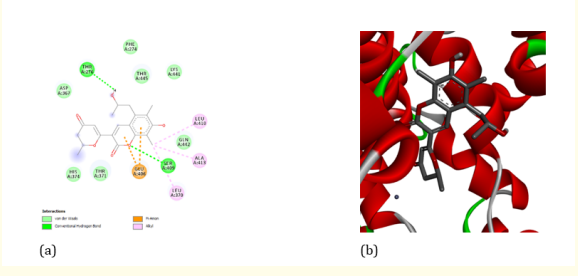

Figure 14: (a) Results of 2D docking of Monankarin E and (b) 3D with 6VW1 protein.

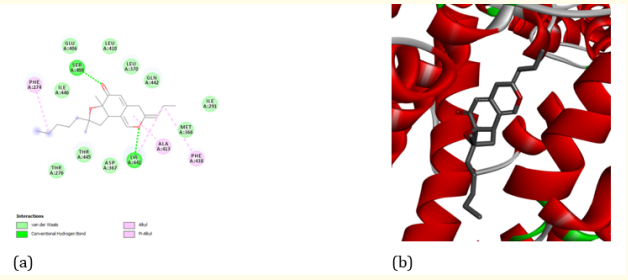

Figure 15: (a) Results of 2D docking of Monapurones C compounds and (b) 3D with 6VW1 protein.

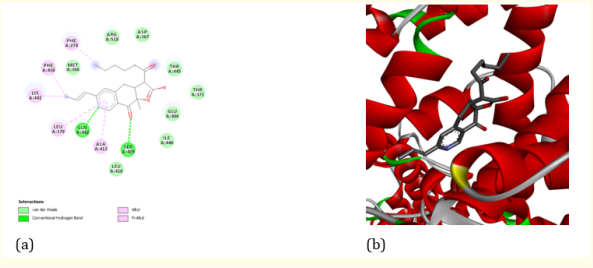

Figure 16: (a) Results of 2D docking of Monascopyridine C and (b) 3D compounds with 6VW1 protein.

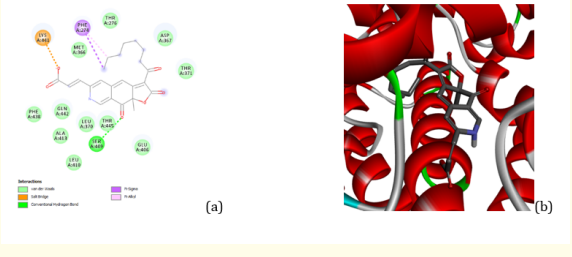

Figure 17: (a) Results of 2D docking of PP-V compounds and (b) 3D with 6VW1 protein.

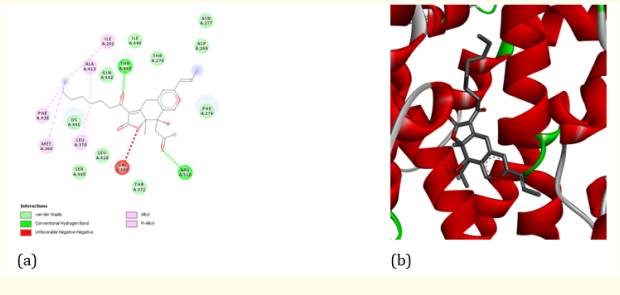

Figure 18: (a) Results of 2D docking of Monaphilol 1C and (b) 3D with 6VW1 protein.

Compound Name	Binding Affinity (Kca/mol)	Hydrogen Bond	Amino acid
Kode 5LHD			
Ligan Alami	-3.4	SER758	CYS761, ASN799, SER762, THR795, CYS798
Monankarin A-B	-8.6	SER670, ASN663	TYR704, ALA445, LYS943, LEU568PHE705, PHE666, SER701, ASN667, SER700, TYR441, LEU437, ARG442
Monankarin C-D	-8.7	ASN663	SER701, SER700, LEU437, TYR441, ARG442, TYR704, LEU568, ALA445, LYS943, SER670, ASN667, PHE666,
Monankarin E	-8.7	SER670, ASN663	SER701, ASN667, SER700, LEU437, TYR441, ARG442, ALA445, TYR704, LYS943, PHE666
Monankarin F	-8.3	-	SER703, TYR704, LEU707, ARG907, MET708, ASN947, LYS943, THR906, ALA940, ALA936, GLN903, GLN939, ALA445, LEU449, VAL446, LEU568
Unamed	-7.4	SER701, ASN667, ARG631, ASN663	ALA445, TYR441, LEU437, SER700, SER703, LYS943, TYR704, SER670, LEU702, PHE705, LEU568, PHE666,

Kode 6VW1			
Ligan Alami	-3.2	PRO284, LYS247 TYR243	PHE285, VAL283, TRP594
Monankarin E	-7.3	SER409, THR276	PHE274, THR445, LYS441, LEU410, GLN442, ALA413, LEU370, GLU406, THR371, HIS374, ASP367
Monapurones C	-7.3	SER409, LYS441	ASP367, THR445, THR276, PHE274, ILE446, GLU406, LEU410, LEU370, GLN442, MET366, ILE291, PHE438, ALA413
Monascopyridine C	-7.2	GLN442, SER409	LEU410, ALA413, LEU370, LYS441, PHE438, MET366, PHE274, ARG518, ASP367, THR445, THR371, GLU406, ILE446
PP-V	-7.3	SER409	LYS441, MET366, PHE274, THR276, ASP367, THR371, GLU406, THR445, LEU410, LEU370, ALA413, GLN442, PHE438
Monaphilol 1C	-7.5	THR445, ARG518	THR371, GLU406.LEU410, SER409, LEU370, LYS441, MET366, PHE438, ALA413, GLN442, LEU291, ILE446, THR276, ASP369, ASN227, PHE274

Table 7: Conclusion of Binding Affinity, Hydrogen Bonds, Amino Acids of natural ligands and test ligands.

smaller of the binding affinity value, then the affinity between receptor and ligand is greater [23]. Thus, it can be analyzed by the following results.

Kode PDB	Grid Box	RMSD	Binding Affinity Ligan Alami (Kca/mol)	Binding Affinity Monankarin E (Kca/mol)
5LHD	X: -36.161 Y: -31.933 Z: 25.394	1.24	-3.4	-8.7
6VW1	X: 114.866 Y: 25.439 Z: 145.547	1.66	-3.2	-7.3

Table 8: Grid Box, Binding Affinity Value of natural ligands and Monankarin E.

Based on the results of docking binding affinity values in the table 8 of both test ligands, they have lower interactions than natural ligands because they have smaller binding affinity values with code receptors of 5LHD and 6VW1. Therefore, it indicates that *Monascus* sp. pigment derivative compound that is Monankarin E has potential activity as an anticorona virus because of its fairly good affinity value.

Molecular dynamic (MOE)

The Dynamic Molecular Process (MD) was performed on the candidate of the test compound that has been performed the process of docking the test ligand with the previous receptor. The best results were obtained in the form of test ligand compounds derived from the pigment *Monascus* sp. that is Monankarin E and its natural ligands by comparison, which has formed a complex with anticorona virus receptors with the 5LHD code. The simulation was conducted using the Molecular Dynamic MOE (Molecular Operating Environment) program.

The simulation was then placed in flexible conditions in the presence of a solvent effect. Solvation born which is an explicit system was a type of solvation used. Since proteins are surrounded by solvents, then the interaction with the solvent system has an impact on the energy produced [31]. The energy minimalization stage was conducted to relax the system by adjusting the position of the atomic geometry, so that the lowest enzyme was obtained for the system [24]. Then the MD simulation was performed at a temperature of 310 K, the addition of this temperature was intended to make the simulation system closer to normal body conditions with the consideration that temperature could affect the stability of the ligand-receptor complex, the MD Simulation was performed for 100 ps [25]. The following are the results of the MD simulation using MOE software with receptor 5LHD code.

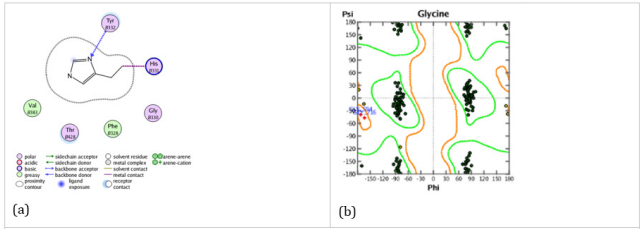

Figure 19: (a) Visualization of MD simulation results of natural ligand compounds (5LHD), (b) Ramanchandran Plot of natural ligand compounds (5LHD) after MD simulation.

Based on the results of the MD simulation in Figure (a), natural ligand compounds experienced changes in the type and amount of contact residues in the tethering area, it can be seen that TYR332, HIS331, GLY330, PHE328, THR428 and VAL383, there are 6 interacting residues, it was caused by the influence of temperature and the presence of solvents in the simulation system, so that there was a changes in the distance between previously interacted atoms. However, these comparison ligands still had interaction with protein and still form a complex between ligand-receptors.

Then, the conformational stability of the protein was seen by using the Ramachandran Plot analysis which was formed as shown in Figure (b). This Ramanchandran Plot analysis was conducted on a complex .pdb file using MOE software. The determination of protein stability can be analyzed for non-glycine residues in the disallowed region of the resulting plot. In figure (b), amino acid residues in the dihedral angle ϕ (psi) the disallowed one (disallowed

region) and the dihedral angel ψ (psi) the allowed one (favorable region) [26]. One of the requirements is that if the non-glycine residue in the disallowed region is more than 15% and the residue in the allowed region is 80%, then the protein structure has a poor structural quality [27].

Category		No of residue	% tage
Most favored region	[A,B,L]	2945	81.6%
Generously allowed region	[~a, ~b, ~l, ~p]	487	13.4%
Disallowed region	[XX]	177	4.9%

Table 9: Ramchandran Plot statistics after natural ligand MD (5LHD).

Based on the results in table 9 that natural ligands has residue in the disallowed region of less than 15% and has residue in the allowed region of 80%, so that they have very good structural quality.

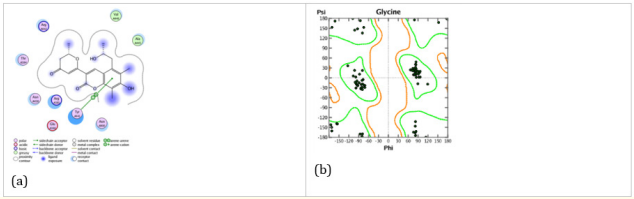

Figure 20: (a) Visualization of MD simulation results of Monankarin E (5LHD) test ligand compound, (b) Ramanchandran Plot of Monankarin E (5LHD) test ligand compound after MD simulation.

The results of the MD simulation is in figure (a), the Monankarin E test ligand compound experienced ligand-protein interactions, it can be seen that ARG442, TYR441, ALA445, VAL446, ASN900, GLU380, ARG381, ASN438 and THR384 there are 9 residues interacted and experienced changes in type and the number of contact residues in the tethering area, it was caused by the influence of temperature and the presence of solvent in the simulation system, so that there is a changes in the distance between previously interacting atoms. However, this Monankarin E compound still has interactions with proteins and still forms complexes between ligand-receptors. Then, the conformational stability of the protein using the Ramachandran Plot analysis was formed as shown in figure (b).

Category		No of residue	% tage
Most favoured refion	[A,B,L]	1598	88.6%
Generously allowed region	[~a, ~b, ~l, ~p]	160	8.8%
Disallowed region	[XX]	44	2.4%

Table 10: Ramchandran Plot statistics after MD ligand assay Monankarin E (5LHD)

Based on the results in table 10, the Monankarin E test ligand has a residue in the disallowed region of less than 15% and has a residue in the allowed region of 80%, so that it has a very good structural quality.

Nama Senyawa	Ikatan Asam Amino
5LHD	
Ligan Alami	TYR332, HIS331, GLY330, PHE328, THR428 VAL383
Monankarin E	ARG442, TYR441, ALA445, VAL446, ASN900, GLU380, ARG381, ASN438, THR384

Table 11: Amino acid binding results after MD of natural ligands and Monankarin E with 5LHD. Receptors.

Conclusion

Based on the research results, it can be concluded that the results of research on compounds derived from the pigment *Monascus* sp. of the 57 derivative compounds that can bind and interact with the ligand-receptor which is the compound Monankarin E (5LHD: -8.7), so that it has a good potential activity as an anticorona virus compared to its comparison compound, which is a natural ligand (5LHD: -3.4) from anticorona virus receptors with 5LHD and 6VW1 codes based on in Silico study.

Competing Interest

The authors declares that they have no competing interest.

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The authors conducted the study without external funding.

Data Availability

Data for this study will made available upon request.

Consent for Publication

All authors have read and approved submission of this research article.

Bibliography

1. Davies PDO. "Multi-drug resistant tuberculosis". *CPD Infection* 3.1 (2020): 9-12.
2. RI KK. "Pedoman Kesiapsiagaan Menghadapi Infeksi COVID-19". *Kementerian Kesehatan Republik Indonesia* 75 (2020).
3. WHO. "WHO Coronavirus Disease (COVID-19) Dashboard". Indoneisa (2020).
4. Yuliana A., *et al*. "Derivates of azaphilone Monascus pigments". *Biocatalysis and Agricultural Biotechnology* 9 (2017): 183-194.
5. Ruswanto. "Molecular docking empat turunan isonicotinohydrazide pada mycobacterium tuberculosis enoyl-acyl carrier protein reductase (InhA)". *Jurnal Kesehatan Bakti Tunas Husada Jurnal Ilmu-ilmu Keperawatan Analis Kesehatan dan Farmasi* 13.1 (2015): 135-141.
6. Ruswanto R., *et al*. "Sintesis Dan Studi *in Silico* Senyawa 3-Nitro-N'-. (Pyridin-4-Yl) Carbonyl]Benzohydrazide Sebagai Kandidat Antituberkulosis". *Chimica et Natura Acta* 3.2 (2015).
7. Rastini MBO., *et al*. "Molecular Docking Aktivitas Antikanker Dari Kuersetin Terhadap Kanker Payudara Secara *in Silico". J Kim* 180 (2019).
8. Moe M. "Molecular Operating a environment" 8 (2019): 99-117.
9. Abdullah M., *et al*. "The effect of ethanolic leaves extract of soursop (*Annona muricata* L.) on human colorectal cancer cell line: cell viability and *in silico* study to cyclin D1 protein". *Health Science Journal of Indonesia* 10.2 (2019): 96-102.
10. Ruswanto R. "Desain dan studi interaksi senyawa n'-(3,5-dinitrobenzoyl)-isonicotinohydrazide pada mycobacterium tuberculosis enoyl-acyl carrier protein reductase". *Jurnal Kesehatan Bakti Tunas Husada Jurnal Ilmu-ilmu Keperawatan Analis Kesehatan dan Farmasi* 14.1 (2015): 1-7.
11. B Fernandes T., *et al*. "Analysis of the Applicability and Use of Lipinski`s Rule for Central Nervous System Drugs". *Letters in Drug Design and Discovery* 13.10 (2016): 999-1006.
12. Adriani. "Prediksi Senyawa Bioaktif dari Tanaman Sanrego (Lunasia amara Blanco) sebagai Inhibitor Enzim Siklooksigenase-2 (COX-2) melalui Pendekatan Molecular Docking". 1 (2018): 6-11.
13. Sulastri S., *et al*. "Studi *In Silico* Senyawa Turunan Flavonoid terhadap Enzim HMG- CoA Reduktase". *Jurnal Mahasiswa Farmasi Fakultas Kedokteran UNTAN* 4.1 (2019).
14. Noviardi H and Fachrurrazie F. "Potensi Senyawa Bullatalisin Sebagai Inhibitor Protein Leukotrien a4 Hidrolase Pada Kanker Kolon Secara *in Silico*". *FITOFARMAKA Jurnal Ilmiah Farmasi* 5.2 (2015): 65-73.
15. Cramer GM., *et al*. "Estimation of toxic hazard-A decision tree approach". *Food and Cosmetics Toxicology* 16.3 (1976): 255-276.
16. Lapenna S and Worth A. "EUR 24898 EN - Joint Research Centre - Institute for Health and Consumer Protection: Analysis of the Cramer classification scheme for oral systemic toxicity-implications for its implementation in Toxtree". *JRC Scientific and Technical Reports* (2011): 39.
17. Kroes R., *et al*. "Structure-based thresholds of toxicological concern (TTC): Guidance for application to substances present at low levels in the diet". *Food and Chemical Toxicology* 42.1 (2004): 65-83.
18. Benigni R., *et al*. "The Benigni/Bossa rulebase for mutagenicity and carcinogenicity - a module of Toxtree". *Heal San Fr* (2008).

19. Saputra DPD. "Molecular Docking Sianidin dan Peonidin sebagai Antiinflamasi pada Aterosklerosis Secara *In Silico*". *Jurnal Farmasi Udayana* 7.1 (2018): 28.

20. Aziz FK., *et al*. "Hasil *In Silico* Senyawa Z12501572, Z00321025, SCB5631028 dan SCB13970547 dibandingkan Turunan Zerumbon terhadap Human Liver Glycogen Phosphorylase (1l5Q) sebagai Antidiabetes". *J Kim Val* 2.2 (2016): 120-124.

21. Arwansyah Ambarsari L and Sumaryada TI. "Simulasi Docking Senyawa Kurkumin Dan Analognya Sebagai Inhibitor Enzim 12-Lipoksigenase". *Current Biochemistry* 1 (2014): 36-39.

22. Saputri KE., *et al*. "Docking Molekular Potensi Anti Diabetes Melitus Tipe 2 Turunan Zerumbon Sebagai Inhibitor Aldosa Reduktase Dengan Autodock-Vina". *Clinica Chimica Acta* 4.1 (2016): 16.

23. Pantsar T and Poso A. "Binding affinity via docking: Fact and fiction". *Molecules* 23.8 (2018): 1DUMMY.

24. Dewi RT., *et al*. "The Applicability of the Crystal Structure of Termotoga Maritima 4- A - Glucanotransferase As the Template for Sulochrin As A -Glucosidase". *Indonesian Journal of Chemistry* 9.3 (2009): 487-490.

25. Maier JKX and Labute P. "Assessment of fully automated antibody homology modeling protocols in molecular operating environment". *Proteins: Structure, Function, and Bioinformatics* 82.8 (2014): 1599-1610.

26. Ho BK and Brasseur R. "The Ramachandran plots of glycine and pre-proline". *BMC Structural Biology* 5 (2005): 1-11.

27. Suhadi A., *et al*. "Simulasi Docking Senyawa Aktif Daun Binahong Sebagai Inhibitor Enzyme Aldose Reductase". *Jurnal Penelitian Kesehatan* 6.2 (2019): 55-65.