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In silico anticholesterol of Monacolin from *Monascus* sp. on HMG-CoA protein receptor

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Abstract

Monascus sp. has traditionally been used in fermenting red rice (angkak) which is useful as a food coloring, food preservative and medicine. Currently, Angkak rice has become a well-known dietary supplement because of the many bioactive compounds it contains such as monacolin. The purpose of this study was to determine the activity of monacolin compounds as anticholesterol, as well as predict the toxicity of compounds through in silico studies. The test compound consisted of 14 monacolin compounds. The protein HMG CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase is used as an anticholesterol receptor. Toxicity prediction and docking results showed that monacolin L has the best anticholesterol activity against HMG CoA reductase. The molecular dynamic results show that monacolin L is stable, it has a low conformational energy value of -10.22 kcal/mol and there are two amino acids that form hydrogen bonds with the active site of the receptor namely Arg A:568 and His A:752, and has 5 acid residues namely Ser A:565, Leu A:853, Arg A:568, His A:752, Leu A:562.

1. Introduction

Hypercholesterolemia is an increase in cholesterol levels in the blood (Soliman, 2018). This disease is characterized by an increase in cholesterol levels exceeding the normal threshold (>240 mg/dl) (Singgih *et al.,* 2019). Hypercholesterolemia occurs in both developed and developing countries, including Indonesia. Hypercholesterolemia is one of the risk factors for cardiovascular disease (Formisano *et al.*, 2019). According to WHO (2017), in 2008, the global prevalence of elevated total cholesterol in adults was 39% (37% for men and 40% for women).

Monascus sp. is a mold that is used to ferment rice to produce red rice (Red Mold Rice) (Nguyen *et al.,* 2017). Red yeast rice is the result of rice fermentation by *Monascus* sp. through a solid fermentation system that appears in red color. The red yeast rice fermentation process produces several secondary metabolites, such as Monacolin K, pigment and citrinin (Yuliana and Apriyani, 2018). *Monascus* sp. is a fungi that is known to produce pigment through a fermentation process in solid or liquid culture. *Monascus* sp. produces pigments which are divided into two, intracellular pigments (water insoluble) and extracellular pigments (water soluble) (Fadillah *et al*., 2020). The main pigment components produced by *Monascus purpureus* are a mixture of yellow, orange and red colors, yellow pigments are included in monascin and ankaflavin; orange pigments are included in monascorubrin and rubropunctatin; and red pigments are included in monascorubramin and rubropunctamin (Yuliana and Arianti, 2020).

Monacolin is a polyketide-derived compound that has the ability to lower lipid levels in the blood. One of the monacolin compounds that has been widely studied is monacolin K (Sabry, 2015). Monacolin K is commercially called Lovastatin, Mevinolin or Mevacor. It has been proven as a specific inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase in cholesterol biosynthesis which helps lower blood pressure. The enzyme reductase is an important key in the synthesis of cholesterol, which produces mevalonyl-CoA. Lovastatin, Mevinolin and Mevacor, as statin drugs, are used in the United States, and have cholesterol synthesis inhibitory characteristics and the same structure as monacolin K (Kraboun *et al*., 2019). One study showed that Monacolin K produced by *Monascus* sp. was proven as an anticholesterol (Singgih *et al*. 2019). Several studies have shown that *Angkak* containing 5-10 mg of monacolin K can lower LDL-C levels by 22 to 27% (Heinz *et al*., 2016).

The *in silico* method has the advantage of being cheaper and faster to produce results. Great efforts have

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been focused on developing computational approaches to scientific research such as toxicity prediction (Makatita *et al*., 2020). The *in silico* toxicology method is able to provide an overview of information related to the toxicity of a compound and help identify the compound to develop new drug candidates. This method is also a complement in *in-vitro* and *in-vivo* tests, to minimize the use of animals, costs and time (Raies and Bajic, 2016). In addition, this study aimed to determine the effectiveness of fourteen monacolin compounds that act as anticholesterol with an *in silico* study.

2. Materials and methods

The test compound was obtained from PubChem based on experimental data from several scientific studies, they were 14 monacolin compounds. The data on the 3D crystal structure of the protein used for molecular anchoring was obtained from the Protein Data Bank (PDB), which was HMG CoA reductase receptor (PDB Code: 1HW9). The hardware used was a laptop with an Intel® Celeron® Quad Core Processor N4120 CPU @ 1.6 GHz 8GB RAM. The software used was ChemDraw 3D, MarvinSketch, DrugScan, PreADMET, pkCSM, Autodock 4.2.6, PDBSum, Discovery Studio 2017 and MOE (Molecular Operating Environment).

The test compound for which molecular anchoring will be carried out was first optimized by using the MarvinSketch software. It was conducted through protonation at pH 7.4 and a conformational search was done to get the most stable position that can interact with the active site on the receptor that would be tested.

Drug observation was conducted on each monacolin compound from *Monascus* sp. Drug observation analysis was carried out by considering Lipinski's rule of five and bioavailability. The parameters used were molecular weight 500 g/mol, lipophilicity 5, hydrogen bond donor 5, hydrogen bond acceptor 10, and refractory molar 20-130 (Ruswanto *et al*., 2017).

2.1 preADMET

preADMET was conduted by using a web-based online program that can be accessed via http://preadmet.bmdrc.org/. All compound structures were converted into molfile format (*.mol). In this study, the permeability of Caco-2 cells (Carcinoma colon bilayer), %HIA (Human Intestinal Absorption) and plasma protein binding (PBB) were used. For toxicity parameters, the carcinogenic and mutagenic properties of these compounds were observed (Ruswanto *et al*., 2017).

The structure of 14 monacolin compounds was translated into SMILES format using the assistance the Online SMILES Translator (https://cactus.nci.nih.gov/translate/). In this SMILES format, the compounds were processed by using the pkCSM online tool (http://biosig.unimelb.edu.au/pkcsm/prediction) to predict the toxicity of compounds (Ruswanto *et al*., 2017).

Receptor identification was conducted by using compound preparations that had been obtained through MarvinSketch, then it was uploaded via the PDBSum web, after inputted, it would give the results in the form of a Ramachandaran plot. Then, the receptor with the selected PDB code was then downloaded through http://www.rcsb.org (Ruswanto *et al*., 2017).

Validation was done by using the redocking method with natural ligands found in the receptor. The molecular docking process was conducted by re-tethering the natural ligand to its receptor through Autodock 4.2.6 software. The parameter used to assess the validity was the Root Mean Square Deviation (RMSD) value of the best ligand conformation from the redocking result, which was the deviation value of the docking ligand space position compared to the crystallographic ligand position. The expected output was the RMSD value that is less than 2.0 and it is declared valid (Ruswanto *et al*., 2017).

The docking was done by using Autodock Tools software by downloading the anticholesterol receptor test from PDB (Protein Data Bank). The result was selected based on which has a low binding affinity value, then the docking process could be seen from the interaction between the ligand and the receptor (Kurniawan *et al*., 2018).

Molecular dynamics simulation of protein test ligand complex was obtained from docking by using MOE software version 2010. The simulation temperature was 310 K (normal temperature of the human body) (Kurniawan *et al*., 2018).

3. Results and discussion

Drug Scan/Ligan Based Drug Likeness is a qualitative concept that describes the similarity of a compound as a drug candidate, such as the complex balance of various molecular properties and structural features that determine whether a particular molecule is similar to a known drug. These molecular properties are mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecular size, flexibility and other pharmacophore properties that affect the behavior of molecules in living organisms, including bioavailability, delivery properties, an affinity for proteins, reactivity, toxicity, other metabolic stability. The Lipinski rule of five can be used to determine the pharmacokinetics of a compound as a drug candidate.

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Lipinski rule of five can help distinguish between drug-like and non-drug-like molecules by considering their absorption rate and permeability through the lipid bilayers of the human body (Tambunan *et al*., 2012).

Lipinski's rule aims to look at the probability of systemic absorption qualitatively (Lipinski *et al.* 1997). Lipinski's rule of five are (1) molecular weight <500 g/mol, (2) lipophilicity <5, (3) hydrogen bond donor <5, (4) hydrogen bond acceptor <10, (5) and molar refractory between 40-130 (Lipinski *et al*., 1997). The physicochemical properties of the 14 monacolin compounds (Table 1) based on the Lipinski rule of five were used to determine the character of a compound being hydrophobic or hydrophilic to pass through the cell membranes by passive diffusion. All monacolin compounds have a molecular weight of less than 500 g/mol which means that the molecules can diffuse through cell membranes by passive diffusion. The number of hydrogen bond donors and acceptors indicates the higher the hydrogen bonding capacity, the higher the energy required for the absorption process to occur. Of 14 monacolin compounds, there were 3 monacolin compounds that did not meet the Lipinski rule of five, they were monacolin K, monacolin P and monacolin O. The log P values of the three monacolin compounds were >5, in other words, the more hydrophobic the molecules are, these compounds will stay longer in the lipid bilayer and more widely distributed in the body, the selectivity of binding to the target enzyme is reduced and causes higher toxicity (Kelutur *et al*., 2020). Molar refractory value provides information about the polarity of the compound. This parameter was evaluated to analyze the drug delivery properties. The monacolin K, O and P compounds have molar refractories that exceed the required value range of 40-130, which means that these compounds have a total polarizability value that is not easy to form into an instantaneous dipole or induce a molecule (Tambunan *et al*., 2012). Thus, it can be concluded that from the 14 monacolin compounds, 3 monacolin compounds that did not meet the Lipinski rule of five were eliminated, they were monacolin K, monacolin O and monacolin P.

ADME testing used the preADMET program quantitatively to predict pharmacokinetic properties in the body in *in-silico*. Generally, the ADME process aims to predict the process of absorption of a drug (absorption), the process of spreading a drug to all body tissues through the blood (distribution), metabolized in certain organs, especially the liver (metabolism), then excreted from the body (excretion) (Shargel *et al*., 2012). Toxicity aims to determine whether there is a toxic effect or not from the test compound (Ruswanto *et al*., 2019).

The absorption process in the human intestine is included in a good range if it is a range of 70-100%. Based on the results of the ADME test using the web-based PreADMET program, Table 2 shows that 11 monacolin compounds have a moderate permeability value ($CaCO_2$) which is in the range of 4-70% explaining the active and passive diffusion transport of a drug molecule. the HIA value was used to predict the percentage of absorption of a drug in the human intestine, showing that 11 monacolin compounds are appropriate which was in the 70-100% range so it can be predicted that these compounds can reach the target location optimally (Suherman *et al*., 2020). Plasma binding proteins (PPB) that are strongly bound to plasma proteins in the body >90% are monacolin L, monacolin L, monacolin J, monacolin L carboxylate, monacolin M, monacolin N, monacolin Q, monacolin R, monacolin X,

Table 1. Drug scan test results according to Lipinski's rule of five.

No	Compound	Parameters				
		Molecular Weight	Hydrogen Donor	Hydrogen Acceptor	Log P	Refractory Molar
		<500 g/mol	<5	<10	<5	40-130
1	Monacolin J acid	338	2	5	3.85	97.74
2	Monacolin L acid	322	1	4	4.14	96.91
3	Monacolin J	320	2	4	3.33	95.49
4	Monacolin J carboxylate	337	1	5	4.09	97.15
5	Monacolin K	404	1	5	5.29*	121.10
6	Monacolin L	304	1	3	4.22	94.67
7	Monacolin L carboxylate	321	0	4	4.38	96.33
8	Monacolin M	406	2	6	4.30	116.46
9	Monacolin N	304	1	3	4	94.67
10	Monacolin O	468	1	8	5.201*	130.24*
11	Monacolin P	484	1	8	6.04*	137.88*
12	Monacolin Q	282	1	2	3.69	86.29
13	Monacolin R	304	1	3	4.04	94.00
14	Monacolin X	418	1	6	4.95	119.56

*Indicate that the compound does not meet the Lipinski rule of five.

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Table 2. ADMET test prediction results.

No	Compound	Absorption		Distribution PPB (%)
		$CaCO_2$ (nm/s)	HIA (%)	
1	Monacolin J acid	19.22	82.83	88.99
2	Monacolin L acid	20.1015	91.72	100
3	Monacolin J	15.91	92.43	98.56
4	Monacolin J carboxylate	19.30	82.87	83.31
5	Monacolin L	26.1674	95.30	100
6	Monacolin L carboxylate	20.185	91.73	100
7	Monacolin M	14.75	93.29	93.64
8	Monacolin N	26.36	95.30	100
9	Monacolin Q	51.81	100	100
10	Monacolin R	27.78	95.30	100
11	Monacolin X	17.92	96.47	92.14

- $CaCO_2$: Low < 4, currently 4-70, tall > 70 nm/s
- HIA: Bad 0-20%, currently 20-70%, good 70-100%
- PPB: Strongly bound >90%, Weakly bound <90%

while those bound weakly at <90% indicates a weak bond with plasma proteins in the body, namely monacolin J acid, monacolin J carboxylate. PPB is an important factor that affects the pharmacokinetic and pharmacodynamic properties of a drug. Therapeutic compounds which are unbound to blood components are free to diffuse across the cell membranes into the active sites and then metabolized by the liver. PPB information is also helpful to estimate metabolism-related drug-drug interactions (DDI) if two drugs are used at the same time. Values of % PPB < 90% were classified as low, values ≥ 90% were classified as high. Once you get to > 99% bound then plasma protein binding is likely to have a significant impact (Nursamsiar *et al*., 2016).

Toxicity testing to determine mutagenic, carcinogenic, and hepatotoxic properties was done using pkCSM (Zaidan *et al*., 2019), aimed to predict and optimize the pharmacokinetic properties and toxicity. The performance of the pkCSM software in the external validation dataset shows an accuracy of 83.8% in the mutagenicity test (Pires *et al.*, 2015). The results of the toxicity prediction of the test compounds with pkCSM are shown in Table 3, there are 11 monacolin compounds in the ames test that were not mutagens and would not act as carcinogens.

The maximum tolerated dose in humans is between -0.302 to 0.833 mg/kg/day. For oral toxicity in rodents (LD50) of the compound monacolin L, an in-silico test was conducted and the classification of the toxicity of the compound was based on the Globally Harmonized System (GHS) by using the Protoxonline tool. LD50 is the amount of compound that can cause the death of 50% of the experimental animal group. From Table 3, it can be seen that all monacolin compounds are predicted to have LD50 values in rodents ranging from 1.595 to 2.482 mol/kg. However, there are three compounds that have hepatotoxicity, monacolin J acid, monacolin acid and monacolin J carboxylate. It indicates that these three compounds can be toxic to the liver. Therefore, the three compounds are eliminated due to their hepatotoxicity (Schmitz *et al*., 2008).

Identification of receptors for monacolin compounds was conducted by using the PDBsum program. PDBsum

Table 3. Toxicity prediction results with pkCSM.

No	Compound	Ames Toxicity (YES/NO)	Max. tolerated dose (human) (log mg/kg/day)	Oral Rat Acute Toxicity (LD50) (mol/kg)	Hepatotoxicity (YES/NO)
1	Monacolin J acid	NO	0.833	2.482	YES
2	Monacolin L acid	NO	-0.032	1.697	YES
3	Monacolin J	NO	0.093	1.922	NO
4	Monacolin J carboxylate	NO	-0.143	1.595	YES
5	Monacolin L	NO	0.043	1.948	NO
6	Monacolin L carboxylate	NO	-0.194	1.629	NO
7	Monacolin M	NO	-0.255	2.238	NO
8	Monacolin N	NO	-0.179	1.809	NO
9	Monacolin Q	NO	0.485	2.482	NO
10	Monacolin R	NO	-0.42	2.056	NO
11	Monacolin X	NO	-0.302	2.235	NO

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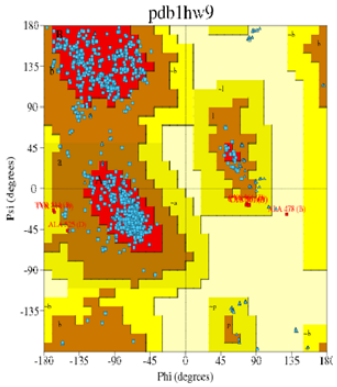
can provide schematic diagrams of the molecules in each structure and the interactions between these molecules. PDBsum used Ramachandran plots to determine protein stability. Ramachandran plots were used to visualize three-dimensional coordinates of proteins obtained from protein structure experiments (Laskowski, 2001). The receptor used was HMG-CoA protein with code 1HW9 and analyzed by using the parameter Plot of Ramachandran as in Figure 1. The result of Plot Ramachandrans analysis showed that the 1HW9 receptor had a stable structure because the residue presentation in the most favored region was 90.0% and 0.1% in the disallowed region. The quality of the protein structure could be stated as good if the residue on the amino acid residue in the most favored region is greater than 50% and the disallow region is less than 15% (Amelia *et al*., 2015).



1. Ramachandran Plot statistics

		No. of residues	%-tage
Most favoured regions	[A,B,L]	1222	90.0%*
Additional allowed regions	[a,b,l,p]	128	9.4%
Generously allowed regions	[~a,~b,~l,~p]	7	0.5%
Disallowed regions	[XX]	1	0.1%*
Non-glycine and non-proline residues		1358	100.0%
End-residues (excl. Gly and Pro)		10	
Glycine residues		151	
Proline residues		64	
Total number of residues		1583	

Based on an analysis of **118** structures of resolution of at least **2.0** Angstroms and *R*-factor no greater than **20.0** a good quality model would be expected to have over **90%** in the most favoured regions [A,B,L].

Figure 1. Plot of Ramachandran protein HMG-CoA code 1HW9.

3.1 Molecular docking method validation

Molecular docking must be validated first to ensure that the docking method used has an accurate geometric pose. The validation was conducted by redocking the natural ligands on each receptor used. Redocking is the process of separating the natural ligand from the crystal structure of the receptor and then redocking it into the receptor. The docking parameter is declared valid if the RMSD value from the redocking results is ≤ 2.0 Å (Kurniawan *et al*., 2018). Based on the results of redocking (Figures 2 and 3), the receptor used in this in-silico study has an RMSD value of < 2.0 Å. This indicates that the AutodockTools software can put back the ligand in its original position with a shift of < 2.0 Å between the natural ligand and the redocked ligand and meets the validity criteria.

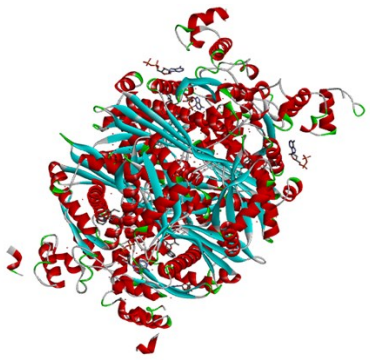


Figure 2. HMG-CoA receptor code 1HW9.

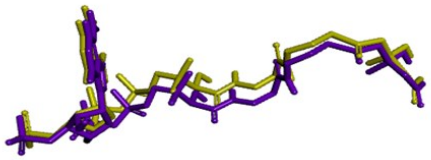


Figure 3. 1HW9 code receptor visualization results (purple) with copy ligand (yellow).

There were 14 monacolin compounds that have been found that were naturally contained in Angkak rice. The picture of monacolin compound structures can be seen in Figure 4. However, only 8 monacolin compounds met the requirements in the DrugScan, preADMET and pkCSM tests. The docking of monacolin compounds was carried out on the HMG CoA reductase receptor to see the anticholesterol activity. The docking of the monacolin molecule will produce a prediction of energy and also a visualized form of interaction pose. Bond free energy (DG) on the calculation result of the mooring by default was correlated with the value of the inhibition

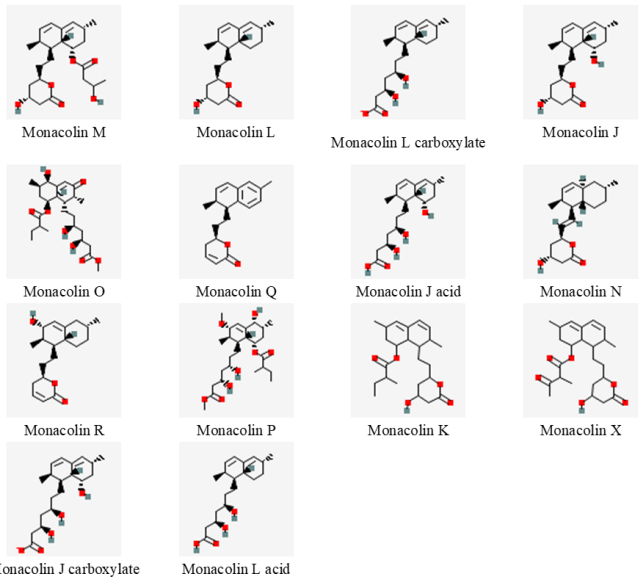


Figure 3. 1HW9 code receptor visualization results (purple) with copy ligand (yellow).

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constant (Ki). Bond energy has a relationship with the constant of inhibition. The smaller the value of the inhibition constant, the lower the bond energy would be. From this, it can be concluded that the lower the bond energy, the more favorable the interaction between the ligand and the enzyme (Masula *et al*., 2018). The calculation of bond-free energy aims to describe the bond affinity and stability of the complex formed. The results of docking and the interaction between ligand and receptor can be seen in Table 4.

Based on Table 4, there are seven monacolin compounds that have lower bond-free energies than their natural ligands, sequentially from the smallest energy, they are monacolin L, monacolin X, monacolin J, monacolin N, monacolin Q, monacolin M, and monacolin R. The smaller the bond free energy value, the more stable the conformation is and vice versa, the greater the bond free energy value, the less stable the conformation will be. The more negative the resulting value, the better the affinity of the protein-ligand complex formed, hence, it is expected that the activity will be even better (Ruswanto *et al*., 2019).

The seven monacolin compounds have a more stable conformation than simvastatin which acted as a natural ligand for the HMG CoA reductase enzyme, so it was expected that the activity of the monacolin compounds could inhibit the work of the HMG CoA reductase enzyme better than simvastatin. The interaction that occurs between the monacolin compound and the HMG CoA reductase enzyme in natural ligands was through hydrogen bonding in Glu559 (Figures 5 and 6). Monacolin L which is the test compound with the best docking results has a similar interaction with natural ligands and was added with another hydrogen bond, namely Ser A:565, which is predicted to cause the more stable conformation of the protein complex with monacolin L.

The compound that was tested for molecular dynamics was monacolin L. Based on the lowest affinity value, the result was -10.22. Simvastatin was used as a control or comparison. Simvastatin belongs to the class of statin drugs that are used as anti-cholesterol drugs. Through this molecular dynamic simulation of the monacolin L compound and the docked positive control, it was expected to find compounds that were stable to thermodynamic changes which can be seen from the conformational energy, hydrogen bonds formed and also by comparing the contact residues from the docking result and molecular dynamic simulations.

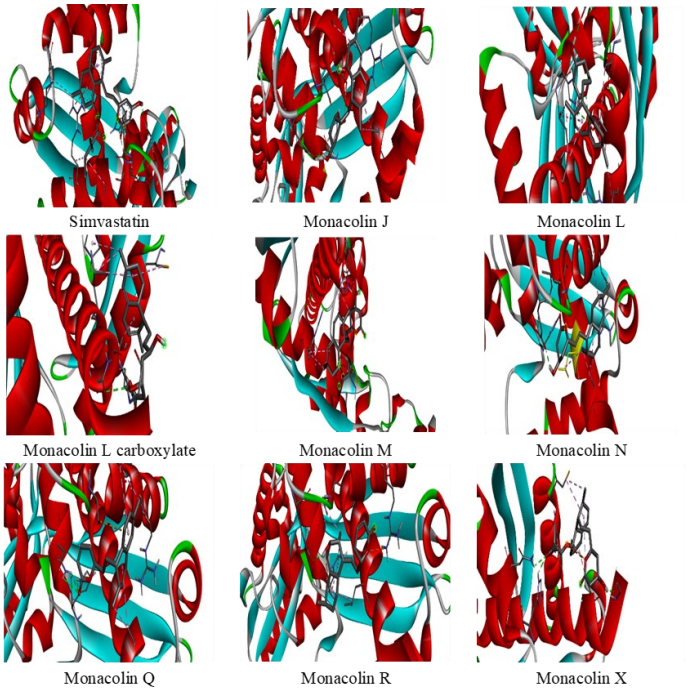

Figure 5. Interaction ligand 3D visualization results.

The considered parameter was the hydrogen bond because in general, the molecular interactions that occur in the body are in the form of non-covalent interactions, which is an interaction between atoms that are not covalently bound to each other. The hydrogen bond is one of the non-covalent bonds that are found in many biological systems, such as proteins and nucleic acids. Hydrogen bonds are the main bonds that maintain protein stability, the hydrogen bond formed in this molecular dynamic simulation indicates compound

Table 4. The results of docking of monacolin compounds on the receptor HMG CoA reductase.

No	Compound	Hydrogen Bond	Binding affinity (Kkal/mol)	Inhibition Constant (nm)
1	Simvastatin	Glu A:559	-9.22	173.12
	Ligand compound			
2	Monacolin J	Glu A:559, Ser A:565	-9.87	58.43
3	Monacolin L	Ser A:565, Glu A:559	-10.22	32.48
4	Monacolin L carboxylate	Gly A:860, Ala A:855	-9.14*	$1.07\times10^{3*}$
5	Monacolin M	His A:752	-9.44	119.89
6	Monacolin N	Glu A:559	-9.72	74.85
7	Monacolin Q	Asn A:755	-9.66	82.46
8	Monacolin R	Glu A:559	-9.37	135.44
9	Monacolin X	Gly A:860, His A:752, AsnA:755, Ser A:565	-10.09	40.00

*Indicate that the compound has a higher binding affinity value than the drug compound simvastatin).

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stability (Frimayanti, 2021).

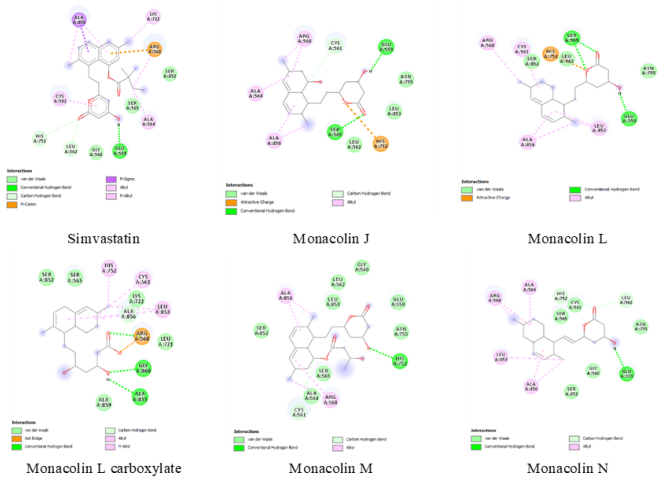
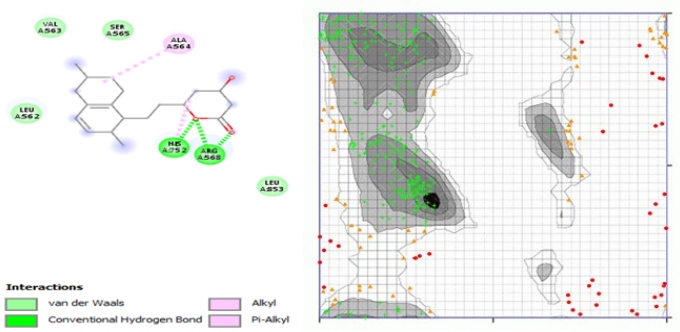


Figure 6. Interaction ligand 2D visualization results.

The match of amino acids to the positive control is also one of the parameters in this molecular dynamic study. The greater the number of amino acids with the same positive control, it can be assumed that the compound has the same or better inhibitory ability with the positive control. During the simulation, there was a change in the interaction between the ligand and the receptor, this caused amino acid residues that were produced in the molecular dynamics and molecular docking was different. The more similar amino acids before and after molecular dynamics, it indicated the more stable the compound and resistance to thermodynamic changes (Frimayanti, 2021).

From the 2D visualization of the Monacolin L compound, it can be seen that the molecular dynamic results compared to the molecular docking results (Table 5) have 5 similar amino acid residues, which were Ser A:565, Leu A:853, Arg A:568, His A:752, Leu A:562, while the similarity of amino acid residues as control amounted to 4 amino acid residues, which were Arg A:568, Ser A:565, Ala A:564, and His A:752. A similar number of amino acid residues of the compound with control amino acid residues was expected to have greater potential as an anti-cholesterol. The hydrogen bond formed in monacolin L compounds was Arg A:568, His A:752, and can be seen in Figure 7.

The dynamic molecular process was conducted on the compound that has the best docking value, that was monacolin L. This simulation was conducted using the 2010 version of the dynamic MOE program. MD simulation is a predictive model of protein-ligand interactions under biological conditions, so the complex model must be set up in an environment that resembles the state of the biological system (Kusuma and Hadi, 2019). The number of non-glycine residues in the disallowed region was 11.396%. The quality of the protein structure is good if the residue in the disallow region (unwanted region) is less than 15% and the amino acid residue in the most favored region is greater than 50% (Table 6) (Amelia *et al*., 2015).



(a) (b)

Figure 7. (a) Ligand interaction on the dynamic molecular compound monacolin L and (b) Ramachandran plots of monacolin L compounds after MD simulation.

Table 6. Ramachandran static plot after MD monacolin compound L.

Category	No of residue	% Tage
Most Favoured region (A, B, L)	249	70.940
Generously allowed region (~a, ~b, ~c)	62	17.664
Disallowed region (XX)	40	11.396

4. Conclusion

The activity of 14 monacolin compounds as secondary metabolites of *Monascus* sp. which has anti-cholesterol the best activity towards HMG Co-A protein, which is monacolin L with a binding affinity of -10.22, and molecular dynamic results with 5 similarities of amino acid residues with molecular docking results; Ser A:565, Leu A:853, Arg A:568, His A:752, Leu A:562, can be used as candidates for new anti-cholesterol drugs.

Table 5. Comparison of docking results with molecular dynamic results.

Compound	Amino Acid Residue		Same Amount
	Results Docking	Results Molecular Dynamic	
Simvastatin (standard)	Glu A:559, Ala A:856, Lys A:722, Arg A:568, Ser A:852, Ser A:565, Ala A:564, Gly A:560, Leu A:562, His A:752, Cys A:561	Val A:563, Arg A:568, Ala A:564, Ser A:565, Ala A:564, Asn A:755, Leu A:561, His A:752, Asn A:755	4
Monacolin L	Ser A:565, Glu A:559, Arg A:568, Cys A:561, Ser A:852, His A:752, Leu A:562, Asn A:755, Leu A:853, Ala A:856	Val A:563, Ser A:565, Ala A:564, Leu A :853, Arg A:568, His A:752, Leu A:562	5

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Conflict of interest

The authors declare no conflict of interest related to this study.

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