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Abstract. Molecular modelling is a technique widely used to understand the properties and activity of molecules in the chemical, pharmaceutical and agrochemical industries. Modelling for macromolecule performed by force field method to find energy and the preferer conformation. Molecular docking method was applied to predict structure of the intermolecular complexes formed between two or more molecules. Molecular structures, dynamics and its interactions is important to determine and understand the function of macromolecule such as peptide or protein. In experimentally previous study the ADTC6 peptide was hypothesized to interact with E-cadherin which able to modify and increase the porosity of tight junction of cell. This study aims to prove the interaction between ADTC6 with E-cadherin and to determine the effect of ADTC6 peptide conformation on binding energy. The first step was the preparation and optimizing of linear and cyclic ADTC6 peptide molecules by molecular dynamics (MD) simulation method with GROMACS (Groningen Machine for Simulation) software. The simulation was done for 20 ns and 120 ns with definite distance parameters and constant restraints between S_{14} atom on Cys1 of ADTC6 and S_{78} atom on Cys6 of ADTC6. The second step was molecular docking between cyclic and linear ADTC6 with E-cadherin in EC1 domain. The result shows that binding energy was changed by different conformation. The lowest energy of linear ADTC6 by MD simulation for 20 ns was -60036.968 kJmol^{-1} (L6) with S_{14}...S_{78} distance was 4.138 Å, and the cyclic was -51747.128 (S2) with S_{14}...S_{78} distance was 2.029 Å. While the lowest energy of linear ADTC6 by MD simulation for 120 ns was -59838.9609 kJmol^{-1} and 17.674 Å. Docking simulation of ADTC6 peptide molecule ... E-cadherin EC1-EC2 domain shows ADTC6 peptide has strong binding energy in *adhesion arm-acceptor pocket* region compared to *bulge-groove* region. Cyclic ADTC6 peptide code S4 as the best conformation in interaction with E-cadherin EC1 because it has binding energy and low inhibition constants, a large population, and a stable pose when re-docking. The cyclic ADTC6 peptide binding energy in the *adhesion arm-acceptor pocket* region and *bulge-groove* region were -27.91 kJmol^{-1} and -21.05 kJmol^{-1}, respectively.

Keywords: E-cadherin, ADTC6, molecular dynamics, molecular docking

1. Introduction

The functions of macromolecules such as proteins and DNA depend on three properties, there are structure, dynamics and interactions [1-4]. These three properties are very important to determine

molecular dynamics and structure because due to their effect on the physicochemical properties of molecules [5]. To understand these three components observed by experiment and computation. Experimentally, sophisticated equipment such as NMR and AFM is required to see atomic and atomic shifts to the level of atoms and electrons. However, the experimental method has the disadvantage of time long consuming and high cost of being able to see atoms to the level of atoms and electrons. Therefore, computational methods are generally applied to connect theoretical chemistry with experiments. Computational methods are applied to determine energy with certain conformations to structures that affect macroscopic material properties. This method is a solution to study the structure, dynamics and interaction of molecules because it has the advantage of short time consuming and reducing costs and support the results of data from experiments [6].

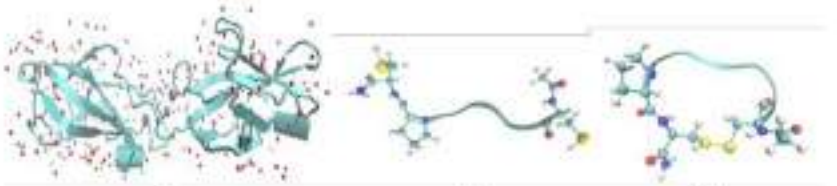
Computational chemistry methods are classified into 3 methods, there are ab initio, semi-empirical and molecular mechanics method [6, 7]. The ab initio method is generally applied because it uses a quantum chemical approach to solve the Schrödinger equation and determine the energy in a molecule. This approach calculates the energy between nucleuses, the nucleus with electrons and electrons with electrons. The ab initio method has a good correlation of results for experiments but this method is just determining the energy of a molecule in a small molecular structure or on a simple system because long time consuming in calculate process. To shorten the calculation time, the QM/MM method was developed with divide the system into two or three different parts using different calculation theories [7, 8]. In this study using a big molecule in large system and looking for the best conformation of ADTC6 peptides, therefore the method of molecular mechanics is used. This method practices a classical approach by calculating atomic energy and ignoring its electronic effects. This approach is sufficient to determine the best conformation of ADTC6 peptides to binding with E-cadherin. Molecular docking method is applied to predict the structure of complex between molecules formed between two or more molecules [9, 10]. Molecular docking is generally used for drug design or structure-based drug design (SBDD) because of its ability to predict the position and orientation of the ligand in binding complex with high-accuracy protein receptors [11].

Treatment of diseases that attack the brain are very difficult because of the blood brain barrier (BBB) as a barrier to the entry of drugs into the brain [12]. The pathway traversed by macromolecular compound is a paracellular pathway, but in this pathway has tight junction which is the most apical component and generally considered a barrier component for paracellular permeability [13]. In order for a molecule to reach the target cell, it must have a diameter of less than 11 Å and a molecular weight less than 500 Dalton [14]. To increase porosity in tight junctions performed by inhibiting the interaction of cadherin-cadherin on the *adherens junction* [15]. Cadherin is a group of transmembrane glycoprotein compounds that find in *zonula adherens*. Cadherin molecule in one cell have homophilic interaction with cadherin molecule in other cells to build *zonula adherens* [16]. Cadherin consists of 5 extracellular domains namely EC1-EC5 which is connected by Ca^{2+} ions which are able to stabilize the structure and interaction on cadherin [17]. Homophilic interaction is the main force in cells adhesion and tight junction formation is an advanced response to this main force. So that disrupting cadherin interactions is expected to widen junction pores between cells [14]. Derivative peptide of cadherin is discovered to be synthesized and able to inhibit cell adhesion in junction between cells [18]. Cyclization is using addition of cysteine groups on ADT6 to form ADTC1 (Ac-CADTPPVC-NH_2) was able to maintain the modulation activity compared to linear ADT6 (Ac-ADTPPV-NH_2), but removal of alanine and valine groups in ADTC1 became ADT6 (Ac-CDTPPC-NH_2) can reduce modulation activity [15]. Previous studies have docking molecules between synthetic cadherin derived peptide and E-cadherin including: 1) docking of HAV5 peptide with EC1 domain of E-cadherin by Makagiansar *et al.* [19] have results HAV5 peptide has binding site on residues 45-52 from E-cadherin and determining that the groove area which is represented by the HAV5 peptide has a counter-sequence in the bulge region [19]. 2) Molecular docking between HAV6 (Ac-SHAVSS-NH_2) and BLG4 (Ac-TYRIWRDTAN-NH_2) peptides with EC5 E-cadherin by Zheng *et al.* [2] have results HAV6 and BLG4 peptides capable of interacting with E-cadherin. The results of the above research can be seen if the derivative peptide of E-cadherin can inhibit the interaction between cadherin-cadherin so that it can increasing porosity in tight junction [2].

Research on ADTC6 has not been carried out in experimentally or computationally, so in this study is observed the between ADTC6 peptides with E-cadherin EC1-EC2 domain with molecular docking method to predict binding energy and binding sites.

2. Methods

E-cadherin EC1-EC2 domain code 2O72 as the host and ADTC6 peptide as guest. ADTC6 linear peptides are made using Pymol software [20]. Meanwhile, the structure of cyclic ADTC6 peptide was performed by forming disulphide bond between S_{γ} and S_{γ} atoms on cysteine amino acid and simple molecular optimization using Avogadro program. The EC1-EC2 domain structure of E-cadherin, Linear and cyclic peptide ADTC6 are depicted in Fig. 1.



(a) (b) (c)

Figure 1. (a) The EC1-EC2 domain structure of E-cadherin, (b) Linear ADTC6 peptide structure, and (c) Cyclic ADTC6 peptide structure.

Table 1. Molecular dynamics variation in ADTC6 peptide.

Code	Linear		
	Distance constraint of S_{16}...S_{78} (nm)	force restraint (kJ/mol^1.nm^2)	Time
L1	All bond freely rotatable	0	20 ns
L2	0.2-0.3	0	20 ns
L3	0.2-0.3	4000	20 ns
L4	0.2-0.3	12000	20 ns
L5	0.3-0.4	0	20 ns
L6	0.3-0.4	4000	20 ns
L7	0.3-0.4	12000	20 ns
L8	All bond freely rotatable	0	120 ns
L9	0.2-0.3	0	120 ns
L10	0.3-0.4	0	120 ns
	Cyclic		
	Distance constraint of S_{16}...S_{78} (nm)	force restraint (kJ/mol^1.nm^2)	Time
S1	All bond freely rotatable	0	20 ns
S2	All bond freely rotatable	4000	20 ns
S3	All bond freely rotatable	12000	20 ns
S4	All bond freely rotatable	0	120 ns

Linear and cyclic peptide ADTC6 was optimize with GROMACS v 4.6.5 using variations of S atomic distances and restraint constants as shown on table 1 for 20 ns and 120 ns. After optimization using GROMACS, best structure of cyclic and linear ADTC6 in 20 ns and 120 ns are calculated binding

energy and binding site with molecular docking simulation using Autodock 4.2 software. Molecular docking divided in 2 stages, there are Autogrid and Autodock. Autogrid stages has function to determine the gridbox on binding site of E-cadherin protein. The Autodock stage performed to find best conformation using the Lamarckian-Genetic algorithm with the number of algorithms executed and the number of evaluations each in the 150 and 10,000,000 sets. The interaction prepared in A and B box, which box A is in *bulge* and *grove* region and box B is in *Thesion arm. acceptor pocket* region and the best position of the binding site and binding energy on the linear and cyclic ADTC6 peptides against the EC1-EC2 domain of E-cadherin was selected.

3. Result and Discussion

3.1. Molecular Dynamic

Molecular dynamic (MD) simulation for ADTC6 linear with a solvent system in 1679 water molecules, 5 Na^+ ions, and 5 Cl^- ions in a 1 nm cube. The results of energy minimization in the system obtained a potential energy of -7.59×10^4 kJmol^{-1} with force of 1.579×10^3 kJmol^{-1}nm^{-1}. Then equilibration is performed in two stages. First, the equilibration of peptide, water and ions for 20 ps with temperature of 300 K and the initial velocity based on the Maxwell distribution have been carried out. Second, the final equilibration of the entire system (linear ADTC6 and solvent) for 100 ps is expected in temperature of 300 K and a pressure of 1 atm. MD is then performed for 20 ns and 120 ns for trajectory production. Trajectory analysis performed RMSD analysis on Cα and total energy analysis. In MD simulation of ADTC6 peptide, RMSD analysis was conducted which aims to determine the movement of peptides dissolved in water and ions by comparing the peptide chain in the native structure of Cα which has the same amount of residue (N) as the alternative structure for 20 ns and 120 ns. The movement of linier ADTC6 peptide as shown in Fig. 2.

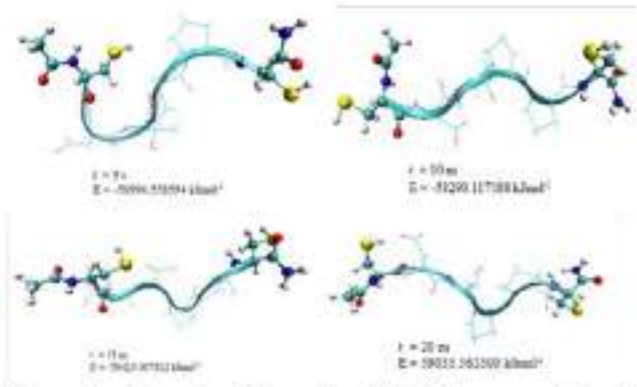
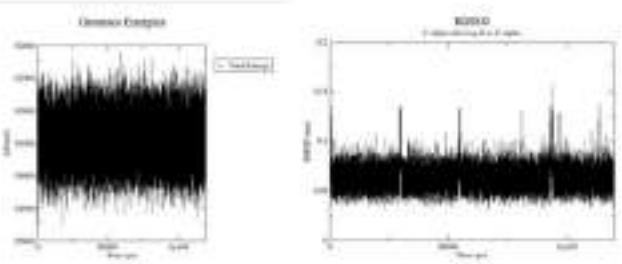


Figure 2. Molecular Dynamic ADTC6 linear peptide at t = 5, 10, 15, 20 ns.

Based on the analysis of total energy and RMSD of Cα in linear and cyclic ADTC6 in the table 2, the peptide movement tends to be stable and does not have many changes due to the force resistance. The RMSD value obtained shows that both linear and cyclic ADTC6 structures tend to be stable because they have RMSD values less than 2 Å. Linear ADTC6 peptide conformation changes can cause peptides to experience folding / unfolding which becomes important because when the peptide undergoes folding it has a more compact and stable structure to its environment or called a native structure. The cyclic ADTC6 peptide has a more compact structure so that interaction with the solvent and structural conformational changes will be reduced because the ADTC6 silk peptide structure loses the rotation of

the chiral atoms due to the peptide backbone structure forming a false ring of sulphide bonds so that the structure orientation is less.



(a) (b)

Figure 3. (a) The total energy graph of cyclic ADTC6 120 ns, (b) The RMSD profile of cyclic ADTC6.

Table 2. Lowest total energy, RMSD, and distance sulphide bond from optimization linier and cyclic ADTC6.

Code	Linear		
	Lowest Total Energy (kJ/mol)	RMSD Cα (nm)	r S_{14}...S_{78} (Å)
L1	-59763.519	0.20 - 0.30	16.955
L2	-59718.746	0.20 - 0.30	12.519
L3	-60012.773	0.15 - 0.20	3.487
L4	-59984.300	0.14 - 0.20	3.305
L5	-60006.937	0.20 - 0.30	15.199
L6	**-60036.968**	**0.14 - 0.18**	**4.136**
L7	-59958.523	0.10 - 0.25	3.514
L8	**-59885.339**	**0.06 - 0.32**	**17.674**
L9	-59685.878	0.07 - 0.32	10.470
L10	-59839.593	0.08 - 0.32	16.095
	Cyclic		
	Lowest Total Energy (kJ/mol)	RMSD Cα (nm)	
S1	-51588.550	0.18 - 0.23	
S2	**-51747.128**	**0.18 - 0.23**	
S3	-51683.734	0.16 - 0.23	
S4	-54750.773	0.03 - 0.16	

In 20 ns MD simulation of linear ADTC6 peptide using 12000 $kJmol^{-1}nm^{-2}$ retaining force provides less stable energy compared to 4000 $kJmol^{-1}nm^{-2}$ restrained force (L4 with L3; L7 with L6) and gives restraint distance S_{14} ... S_{78} of 0.2-0, 3 nm gives a bad impact on peptides, but if the restraint distance is 0.3-0.4 nm, the optimum energy is obtained. This shows that if the given restraining force is too large or the restraint distance is too close, intramolecular contact will be large. But the difficulty of the molecular structure to be oriented causes greater energy/unstable energy. In 120 ns the most stable

ADTC6 linear peptide without variation in distance with the lowest total energy. This structure has a folding form compared to variations in distance sulphide bond 0.2 -0.3 and 0.3 -0.4. The cyclic ADTC6 peptide S2 code is the best structure in a variety of retaining styles based on table 2. This structure has the lowest total energy value of -51747.128 kJmol^{-1} but is less low than the linear ADTC6 peptide L6 code with a value of -59763.519 kJmol^{-1}, this is due to the cyclic ADTC6 peptide S2 code having a ring structure so that freedom of freedom lowest energy. ADTC6 cyclic peptide S2 code has a secondary structure of β-bridge and accessible low protein surfaces showing compact and folding structures. Graph of RMSD cyclic ADTC6 cyclic S2 code is less stable than S3 code, but does not change the candidate as the best structure because the RMSD value is still below 0.3 nm which indicates the cyclic structure of ADTC6 cyclic S2 code is stable during MD simulation. ADTC6 cyclic peptide S4 code has the lowest energy because it uses the 120 ns parameter where more structural conformations are obtained by increasing the simulation time. in MD simulation, the ADTC6 peptide codes L6, L8, S2 and S4 have the minimum energy. This peptide will do molecular docking simulations in A and B box using Autodock 4.2.

3.2. Molecular Docking

Linear and cyclic ADTC6 peptides have C (carbon), HD (hydrogen for hydrogen bonding) atomic types, N (hydrogen unable to bind to hydrogen), OA (hydrogen capable of binding), SA (hydrogen-capable sulfur) and degrees free torsion of linear ADTC6 peptides as many as 18 out of 25 and cyclic as many as 6 of 8. Macromolecular preparations are carried out by removing water and ion molecules. In molecular docking involved two step: 1. Autogrid, 2. Autodock. In Autogrid. In the Autogrid step was performed an evaluation on the EC1 domain of E-cadherin with a gridbox size of 62x62x62 on A-B boxes and grid spacing of 0.425Å for box A and 0.375 for box B. Then, Autodock with the number of evaluation process of 10,000,000 was done as second step. The result is there are 2 best poses for ADTC6 peptide in each box based on the lowest energy, inhibition constants, population, and re-docking results. Based on docking result in table 3, Cyclic ADTC6 peptide code S4 has best interaction in box B in pose 72 with energy binding -27.91 kJ/mol. This binding energy includes moderate bonding energy [21] so that the ADTC6 peptide can interact with E-cadherin to open the tight junction and be released again so that the tight junction can be closed again.

Table 3. Molecular docking of ADTC6 Peptides with EC1-EC2 domain of E-cadherin.

Code	Box	Pose	ΔG (kJ/mol)	Ki (μM)	Population	RMSD (Å)
L6	A	45	-19.79	343.22	1	3.887
		108	-17.94	712.62	1	3.237
	B	4	-23.38	80.29	1	2.712
		29	-21.38	179.99	2	3.244
L8	A	93	-24.52	50.69	8	5.099
		78	-19.66	357.96	5	3.493
	B	27	-19.83	337.99	6	3.944
		131	-16.95	107	4	3.589
S2	A	108	-23.63	71.71	79	0.084
		3	-21.29	186.65	3	3.55
	B	9	-26.98	18.56	62	0.104
		8	-25.94	28.57	57	2.963
S4	A	113	-21.00	208.42	103	3.717
		1	-21.05	205.66	32	3.758
	B	5	-21.97	142.47	71	0.669
		72	-27.91	12.88	24	3.243

Energy binding of ADTC6 code S4 also have two hydrogen bonds shown in table 4. This hydrogen bonds is between Asp2…Lys25 and Pro5…Val3 with a distance of 2.195 and 2.861 Å respectively. The interaction of cyclic ADTC6 peptide code S4 with EC1-EC2 domain from E-cadherin on Trp2, Val3, Ile4, Ile24, Lys25, Asn27, Met92 residues in *adhesion arm-acceptor pocket* region (Fig. 4). Docking of ADTC6 peptide molecules … E-cadherin EC1-EC2 domain shows cyclic ADTC6 peptide S4 code as the best compound in inhibiting E-cadherin EC1 domain with the strongest binding site in the *adhesion arm-acceptor pocket* region then *bulge-groove* region. The results of Siahaan *et al.* [22] study showed that the cyclic ADTC5 peptide had the strongest interaction in the *bulge* region and the *adhesion arm-acceptor pocket* area of the E-cadherin EC1 domain. This shows the similarity in the site of interaction between the two peptides and confirms the statement that E-cadherin has two binding sites on the EC1 domain, namely the *bulge-groove* region and the *adhesion arm-acceptor pocket* region. Comparison of E-cadherin residues that interact with cyclic ADTC6 peptides and cyclic ADTC5 [22] is described in table 5.

Table 4. Hydrogen bond and binding site of ADTC6 peptides.

Code	Box	Hydrogen Bond			Binding Site
		Interaction	r (Å)	Type	
L6	A	Thr3…Tyr36	1.826	OH…O	Tyr36, Ser37, Ile38, Ala43, Asp44, Gly49, Ile52, Ile53, Glu54, Arg55
		Cys6…Ile38	1.931	SH…O	
	B	Thr3…Lys25	2.159	OH…O	Asp1, Trp2, Val3, Ile4, Ile24, Lys25, Ser28, His79, Ala80, Glu89, Asp90, Pro91, Met92
		Cys6…Asp90	2.068	NH…O	
L8	A	Cys1…Ile38	1.762	HN…O	Tyr36, Ser37, Ile38, Asp44, Gly49, Phe51, Ile52, Ile53, Glu54, Glu56, Arg55, Thr57
		Thr3…Ile53	1.694	HN…O	
		Cys6…Glu54	2.005	HT1…OE2	
		Cys6…Glu54	1.796	HN…OE	
	B	Cys1…Asn27	2.137	O…N	Val3, Ile4, Pro5, Val22, Gln23, Ile24, Lys25, Asn27, Glu89, Met92
		Thr3…Lys25	1.959	HG1…N	
S2	A	Cys6…Ile38	1.994	NH…O	Ser37, Ile38, Phe35, Ala43, Asp44, Ile53, Arg55, Val81
	B	-	-	-	Trp2, Ile4, Gln23, Lys25, Ser26, Asn27, Glu89
S4	A	Cys6…Ile38	2.307	HT1…O	Phe35, Tyr36, Ser37, Ile38, Asp44,Arg55, Val81
	B	Asp2…Asn27	2.838	O…ND2	Trp2, Val3, Ile4, Ile24, Lys25, Asn27, Met92
		Asp2…Lys25	2.195	OD2…NZ	
		Pro5…Val3	2.861	O…ND2	

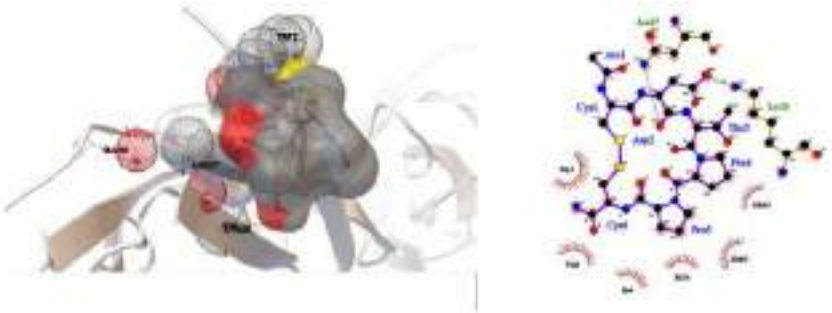


Figure 4. The interaction between cyclic ADTC6 peptide code S4 and the EC1-EC2 domain of E-cadherin with used (a) Autodock program, and (b) Ligplus program.

Table 5. Residues on the cyclic ADTC6 peptide binding site and cyclic ADTC5 with E-cadherin.

Binding Site	Cyclic ADTC6 peptide	Cyclic ADTC5 peptide
adhesion arm-acceptor pocket region	Trp2, Val3, Ile4, Ile24, Lys25, Asn27, Met92	Trp2, Val3, Ile4, Gln23, Ile24, Lys25, Asn27, Met92
bulge-groove region	Phe35, Tyr36, Ser37, Ile38, Asp44,Arg55, Val81	Tyr36, Ile38, Ala43, Asp44, Val48, Gly49, Phe51, Ile52, Ile53, Arg55

Molecular docking of two type of peptide shows 1) Trp2, Ile4, Gln23, Lys25, Asn27. 2) Ile38, Ala43, Asp44, Ile53, Arg55 as E-cadherin residues which are important in interaction with ADTC6 and ADTC5 peptides. The loss of valine sequence in ADTC6 results in reduced ability to interact with hydrophobic E-cadherin residues such as Val3, Ile24, Tyr35, Phe51, Ile53 and strengthens hydrophilic properties to interact with Ser26 and Ser37.

4. Conclusion

Docking simulation of ADTC6 peptide molecule ... E-cadherin EC1-EC2 domain shows ADTC6 peptide has strong binding energy in *adhesion arm-acceptor pocket* region compared to *bulge-groove* region. Cyclic ADTC6 peptide code S4 as the best conformation in interaction with E-cadherin EC1 because it has binding energy and low inhibition constants, a large population, and a stable pose when re-docking. The cyclic ADTC6 peptide binding energy in the *adhesion arm-acceptor pocket* region and *bulge-groove* region were -27.91 kJmol^{-1} and -21.05 kJmol^{-1}, respectively.

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