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Probing the Interaction between Cyclic ADTC1 Ac-CADTPPVC-NH_2) Peptide with EC1-EC2 domain of E-cadherin using Molecular Docking Approach

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Abstract. Deeply understanding that intermolecular interaction between molecules on the paracellular pathway has given insight to its microscopic and macroscopic properties. In the paracellular pathway, synthetic cyclic ADTC1 (Ac-CADTPPVC-NH_2) peptide has been studied to modulate EC1-EC2 domain, computationally using molecular docking method. The aim of this research is to probe the effect of amino acid alanine (A) of ADTC1 on its interaction properties. The study carried out in two steps: 1. the optimization using GROMACS v4.6.5 program and; 2. Determination of the interaction properties using AutoDock 4.2 program. The interaction was done for A-J box, and the best position of the binding site and binding energy on the OC and CC ADTC1 peptides against the EC1-EC2 domain of E-cadherin was selected. The result showed that the CC of the F box ADTC1 has the best interaction with binding energy of -26.36 kJ/mol and its energy was lower than ADTC5 without alanine amino acid. ADTC1 interacted with EC1 of EC1-EC2 on Asp1, Trp2, Val3, Ile4, Ile24, Lys25, Ser26, Asn27, and Met92 residues.

1. Introduction

Intermolecular interaction is a very important study in understanding the nature of a molecule macroscopically and microscopically [1]. This interaction study has been studied computationally using the molecular docking method between cadherin peptides against EC1 and EC5 domains [2-5]. The cadherin peptide is a derivative synthesis peptide of the bulge and groove region sequences in the cadherin, where the bulge region is an ADT structure and the groove region is a HAV structure [6]. This cadherin peptide can be used to modulate intercellular junction by inhibiting cadherin-cadherin interactions [7-9].

In this research has been studied the interaction study between ADT structure with EC1 domain on E-cadherin [10]. Where the ADT structure has several derivatives, one of which is the ADTC1 (Ac-CADTPPVC-NH_2) peptide. This peptide is thought to increase its biological activity in inhibiting cadherin-cadherin interactions. Moreover, previous study has shown that ADTC1 peptide can inhibit cadherin-cadherin interaction with ADT peptide binding on groove region the EC1 domain [11]. However, the biological activity is affected by the structure form of the open-cyclic (OC) and close-

cyclic (CC) ADTC1 peptide, aside from that also influenced by changes in the structure of each time using Molecular Dynamics (MD) simulation for 20 ns (20,000 ps) as shown in Table 1.

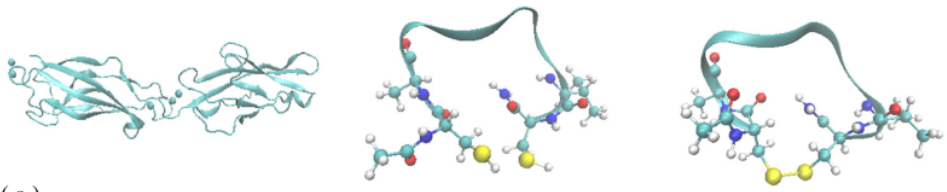
Table 1. Generated OC and CC forms of the ADTC1 peptide by molecular dynamics approach

Code	OC		
	Distance constraint of $S_{14}...S_{105}$ (nm)	force restraint ($kJ/mol^1.nm^2$)	Total Energy (kJ/mol)
A1	All bond freely rotatable	None	-82,504.52
A2	0.2-0.3	None	-82,830.28
A3	0.3-0.4	None	-82,685.92
B1	All bond freely rotatable	4,000	-82,567.45
B2	0.2-0.3	4,000	-82,964.15
B3	0.3-0.4	4,000	-82,869.02
C1	All bond freely rotatable	12,000	-82,638.36
C2	0.2-0.3	12,000	-82,823.03
C3	0.3-0.4	12,000	-82,690.93
	CC		
D1	All bond freely rotatable	None	-59,769.39
D2	All bond freely rotatable	4,000	-59,807.41
D3	All bond freely rotatable	12,000	-59,851.81

Based on Table 1 the formation of CC peptide using OC peptide (code B2) and on the optimization result of CC obtained stable structure CC (code D3) that is by giving force restraint for 12,000 $kJ/mol^1.nm^2$ which result then used for optimization of DM simulation for 120 ns (120,000 ps). Previous studies have performed DM simulations for 120 ns for the ADTC5 peptide and have studied the interaction between the peptide ADTC5 (Ac-CDTPPVC-NH_2) with the EC1-EC2 domain on E-cadherin [12]. Of the two structures of this peptide that distinguish is the amino acid structure, where on ADTC1 peptide there is substitution of alanine amino acid. The aim of this research is to determine the effect of alanine substitution to modulate of EC1-EC2 domain on E-cadherin.

2. Materials and Methods

The structure of OC ADTC1 peptide was built from PyMol program [13]. Meanwhile, the structure of CC ADTC1 peptide was performed by forming disulfide bond between S_{14} and S_{105} atoms on cysteine amino acid and simple molecular optimization using Avogadro program. The EC1-EC2 domain of E-cadherin protein obtained from Protein Databank with ID 2O72. The EC1-EC2 domain structure of E-cadherin, OC ADTC1 peptide, and CC ADTC1 peptide are depicted in Figure 1.



(a) (b) (c)

Figure 1. (a) The EC1-EC2 domain structure of E-cadherin, (b) CC ADTC1 peptide structure, and (c) CC ADTC1 peptide structure.

This study carried out in two steps. The first step was the optimization using GROMACS v.4.6.5 program. The optimization was done for two types of ADTC1 peptide: open-cyclic (OC) and close-cyclic (CC) on 20,000 and 120,000 ps, respectively. The OC and CC affected by its distance constraints and force restraints (Table 1). The most stable peptide was resulted by optimatization on 20,000 ps and the force restraint 12,000 kJ/mol^1.nm^2 applied to the optimatization on 120,000 ps, shown in Table 2. The second step was to determine the interaction properties using AutoDock 4.2 program [14]. The interaction was done for A-J box, and the best position of the binding site and binding energy on the OC and CC ADTC1 peptides against the EC1-EC2 domain of E-cadherin was selected.

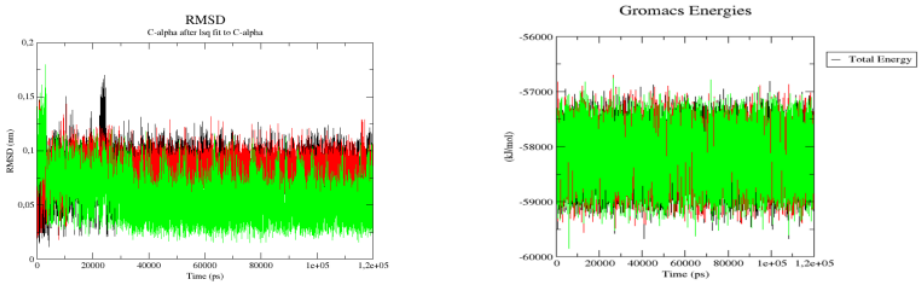
Table 2. Variation of MD simulation the CC ADTC1 peptide for 120 ns

Code	Distance constraint of $S_{14}...S_{105}$ (nm)	force restraint (kJ/mol^1.nm^2)
E1	All bond freely rotatable	None
E2	All bond freely rotatable	4,000
E3	All bond freely rotatable	12,000

3. Result and Discussion

Molecular Dynamic (MD) Simulation

In the MD simulation of CC ADTC1 peptide performed preparation system, trajectory generation, and trajectory analysis. In the preparation system stage was done by adding solvents, ions, minimization energy, molecular dynamics on restraint position, and the unconstrained final equilibrium. The generate trajectory stage was done by MD simulation for 120 ns. In the trajectory analysis stage generated RMSD and total energy. Trajectory analysis performed RMSD analysis on Cα and total energy analysis, as depicted in Figure 2. Based on RMSD analysis of Cα on CC ADTC1 peptide, the movement of peptide molecules tends to be stable and does not undergo much change due to the presence of force restraint (Table 3). Force restraint of MD simulation of the peptide structure $C\alpha_1$ will undergo a non-significant change into $C\alpha_2$. Moreover, it can be proven by the change of distance between $S_{14}...S_{105}$ in the amino acid cysteine as shown in Table 4. Changes in peptide structure of CC ADTC1 affected the structure folding/unfolding, the peptide with folding structure is more stable due to it has the lowest energy [15].



(a) (b)

Figure 2. (a) The RMSD profile, (b) The total energy graph. Where variation force restraint of MD simulation the CC ADTC1 peptide to the black color: code E1 (None), red color: code E2 (4,000 kJ/mol^1.nm^2), green color: code E3 (12,000 kJ/mol^1.nm^2).

Table 3. Generated CC forms of the ADTC1 peptide by molecular dynamics on 120 ns

Code	Total Energy	RMSD

	(kJ/mol)	(nm)
E1	-59,675.75	0.0111 - 0.1702
E2	-59,605.48	0.0177 - 0.1473
E3	-59,851.93	0.0136 - 0.1886

Table 4. The movement of CC Peptide ADTC1 during MD simulation on 120 ns

	E1		E2		E3	
The movement of peptides per ns	Total Energy (kJ/mol)	$R_{S14...S105}$ (Å)	Total Energy (kJ/mol)	$R_{S14...S105}$ (Å)	Total Energy (kJ/mol)	$R_{S14...S105}$ (Å)
0	-57,875.71	2.02974	-57,697.34	2.02891	-57,730.98	2.02907
20	-58,144.59	2.02890	-58,157.43	2.02862	-58,097.78	2.02843
40	-58,422.90	2.02855	-58,450.05	2.02935	-58,522.11	2.02909
60	-57,663.82	2.02936	-57,914.05	2.03290	-57,831.62	2.02962
80	-57,532.91	2.02875	-57,826.46	2.02939	-57,596.36	2.02896
100	-58,574.47	2.02905	-58,335.01	2.02850	-58,494.67	2.02864
120	-58,185.25	2.02829	-58,212.71	2.02917	-58,172.73	2.02940

Furthermore, a total energy analysis was performed on CC ADTC1 peptide. Based on Table 3, optimization with the addition of force restraint 12,000 kJ/mol[1].nm[2] has generated the most stable energy of -59,851.93 kJ/mol. This is due to the effect of providing force restraint that causes rigid peptides structure, degrees of freedom of torque decrease and the probability of interaction with the electrostatic forces of the ions and solvents becomes smaller so that the conformation tends to be more stable. The stable total energy of the structure in code E3 was further investigate its interaction with E-cadherin domain using molecular docking.

Molecular Docking

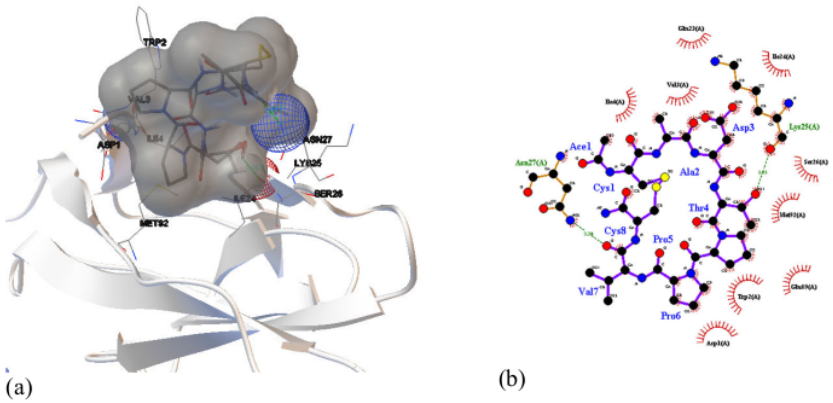
After having obtained stable structure on optimization ADTC1 peptide using GROMACS, molecular docking was performed by using Autodock 4.2 program [14]. The preparation of molecular docking involved two steps: 1. Autogrid and 2. Autodock. In the Autogrid step was performed an evaluation on the EC1 domain of E-cadherin with a gridbox size of 50x50x50 on A-J boxes and grid spacing of 0.375 Å. Then, Autodock with the number of evaluation process of 5,000,000 was done as second step. Based on docking result that CC ADTC1 peptide from box F has the best interaction with binding energy of -24.89 kJ/mol (Table 5). This is also reinforced by the formation of hydrogen bonds between Lys25(O)...Thr4(HG1) and Asn27(ND2)...Cys8(NH) with a distance of 2.033 Å and 2.097 Å respectively. The interaction of CC ADTC1 peptide with EC1-EC2 domain from E-cadherin on Asp1, Trp2, Val3, Gln23, Ile24, Lys25, Ser26, Asn27, and Glu89 residues.

Table 5. Molecular docking of close-cyclic ADTC1 Peptide with EC1-EC2 domain of E-cadherin

Box type	Pose	ΔG (kJ/mol)	Ki (μM)

A	93	-16.15	1. 49 x 10^3
B	31	-14.14	3.31 x 10^3
C	57	-18.70	528.47
D	54	-16.40	1.34 x 10^3
E	131	-13.05	5.2 x 10^3
F	139	-24.89	43.2
G	109	-14.23	3.22 x 10^3
H	99	154.93	-
I	52	17.70	-
J	43	-22.43	118.44

The F box was validated using RMSD value ≤ 2 Å and the obtained binding energy of -26.36 kJ/mol and Ki of 24.09 μM was resulted. Validation results in F box is valid due to the value of RMSD ≤ 2 Å is 0.49 Å. The interaction of CC ADTC1 peptide with EC1-EC2 domain from E-cadherin involved Asp1, Trp2, Val3, Ile4, Ile24, Lys25, Ser26, Asn27, and Met92 residues (Figure 3). In the interaction of CC ADTC1 peptide with EC1-EC2 domain of E-cadherin formed two hydrogen bonds between Lys25(O)...Thr4(HG1) and Asn27(ND2)...Cys8(NH) with a distance of 1.983 Å and 2.177 Å respectively. In the previous study also obtained similar approach in investigating the interaction between ADTC5 peptide with EC1-EC2 domain of E-cadherin [12]. The difference between ADTC1 and ADTC5 peptides is the presence of an alanine amino acids on ADTC1 peptide sequence and the docking results of the interaction between CC ADTC5 peptide and EC1-EC2 domain of E-cadherin can be seen in Table 6.



(a) (b)

Figure 3. The interaction between cyclic ADTC1 peptide and the EC1-EC2 domain of E-cadherin with used (a) Autodock program, and (b) Ligplus program.

Table 6. Molecular docking of close-cyclic ADTC5 Peptide with EC1-EC2 domain of E-cadherin [12].

ADTC5	Pose	ΔG (kJ/mol)	Ki (mm)

B1	26	-16.95	1.08
	57	-16.36	1.36
	73	-12.93	5.41
	147	-13.56	4.22
B2	23	-11.13	11.14
	71	-11.59	9.25
	80	-14.85	2.48
	100	-16.28	1.42
	124	-14.60	2.78
B3	23	-11.72	8.93
	38	-10.46	14.78
	124	-17.45	0.88

Based on Table 5 and Table 6 we can see the difference of binding energy of the CC ADTC1 and ADTC5 peptides. On the CC ADTC1 peptide has lower energy than ADTC5 which was -24.89 kJ/mol for ADTC1 peptide and after validation the binding energy became -26.36 kJ/mol. Meanwhile, the ADTC5 peptide has the lowest binding energy -17.45 kJ/mol. It assumes that alanine affected this interaction. The effect of alanine addition was estimated by the ability of its biological activity to modulate cadherin-cadherin interactions which has greater activity than CC ADTC5 peptide.

4. Conclusion

From the results of this interaction study it is shown that the CC ADTC1 peptide of the F box has the best interaction with binding energy of -26.36 kJ/mol and its energy is lower than the CC ADTC5 peptide. It is estimated that the effect of addition of Alanine amino acid on peptide ADTC1. The interaction of ADTC1 with EC1-EC2 domain from E-cadherin on Asp1, Trp2, Val3, Ile4, Ile24, Lys25, Ser26, Asn27, and Met92 residues.

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8