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Research Article

Molecular Interactions of Renin with Chikusetsusaponin IV and Momordin IIc

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The paper dealt with the molecular mechanism for the binding sites and driving forces of renin with chikusetsusaponin IV and momordin IIc by means of molecular docking and free energy calculation based on the crystal structure. The result showed that renin and the saponins fit well. As shown by LigPlot + software analyzing the hydrogen bonding and hydrophobic effect between renin and the saponins, the amino acid residues such as Ser230, Tyr85, and Tyr201 form the hydrogen bonds, with $S3^{sp}$, S3, and S2′ being the active pockets. In addition, there are relatively strong hydrophobic interactions of renin with saponins in $S3^{sp}$, S3, S2, S1, S1′, and S2′, with Gly228, Val36, Ala229, Gln19, Met303, Gln135, Ser41, Ile137, Asp38, Arg82, and Tyr83 being the key amino acids. The dynamics reached equilibration after about 1000 ps simulation with average root-mean-square deviations of 0.222 nm and 0.217 nm. The molecular mechanics Poisson–Boltzmann surface area (MM-PBSA) yielded −1.10812 kcal/mol and −39.0587 kcal/mol total binding energy for the two complexes, respectively, which were primarily contributed by electrostatic and van der Waals interaction energies, and the binding was strongly unfavored by polar solvation energy, a further confirmation that momordin IIc has stronger hydrogen bonding and hydrophobic effect in the inhibition of renin than the chikusetsusaponin IV.

1. Introduction

Complications such as hypertension, cardiovascular disease, and coronary heart disease are mostly caused by excessive activation of the renin-angiotensin system (RAS), which is mainly composed of angiotensinogen (AGT), renin, angiotensin-converting enzyme (ACE), angiotensin I (Ang I), angiotensin II (Ang II), and its receptors such as AT1 (AT1R) and AT2 (AT2R) [1, 2]. Angiotensinogen, under the effect of renin, is enzymatically hydrolyzed into a deficient Ang I which is cleaved by ACE. In addition, the hydroxy terminal residue is converted into an octapeptide Ang II which is secreted into the target tissue through the blood circulation. Because of its combination with receptors, resulting in vasoconstriction and regular changes in blood pressure, body fluid balance, and electrolyte balance [3], Ang II can be bound to AT1 to cause vasoconstriction and increase blood pressure. Therefore, Ang II is the active hormone in the process and its reduction is of great significance to treat the above-mentioned diseases. Renin, also known as angiotensinogenase or angiotensin-forming enzyme, is the crucial first rate-limiting enzyme that catalyzes the formation of Ang II, and confining its activity can block RAS and Ang II production.

The inhibitors interfere with not only renin but also the amplified physiological effects of prorenin, suggesting that they have unique physiological and pharmacological effects compared to other RAS inhibitors [4]. Although there has been advance in the study of inhibitors of renin in the past years, there has been little progress recently, which, Fisher and Hollenberg believe, is because of the failure to obtain highly active compounds due to the lack of structural system optimization based on the active site [5]. Although aliskiren was the first to be used in clinical practice because it can reduce the renin activity and, in turn, the blood pressure [6], its use has been restricted due to its side effects and inability

to be used on special populations [7]. This is why studies on inhibitors of renin and receptor blockers have been receiving much attention in recent years.

In 2010, Saori et al. [8] found out that there are some legumes that have the inhibitory effect on renin. The inhibitor isolated from soybean was identified as soyasaponin I, an oleanane-type pentacyclic triterpenoid glycoside compound, after the determination of its chemical structure composed of oligosaccharide chain and the nonpolar triterpene aglycone. Studies in China and other countries have confirmed that chikusetsusaponin is mainly composed of oleanane-type triterpene saponins [9]. Modern pharmacological studies have found that ginseng saponins have a variety of biological activities that have certain pharmacological effects on the cardiovascular system, kidney, myocardium, diabetes, and tumors [10, 11]. HPLC of the sample bamboo ginseng from different areas defines ginseng saponins mainly consist of chikusetsusaponin V, chikusetsusaponin IV, and chikusetsusaponin Iva [12], accounting for 3% to 7.9%, 0.2% to 8.6%, and 0.5% to 6.2%, respectively [13]. Although there have been some studies on the nutritional functions of chikusetsusaponin V and chikusetsusaponin IVa and their effects on the cardiovascular system [14–17], the biological activity of the bamboo chikusetsusaponin IV has not been studied, if not published. Some studies show that a dog has increased blood flow in its hind limbs after it is injected in its femoral artery momordica saponin whose leachate has a good antihypertensive effect on animals such as rabbits, dogs, and cats [18]. In addition, a rat experiences short-lived and excited breathing and significantly decreased blood pressure [19]. Momordin Ic and IIc were first isolated by Iwamoto et al. [20], the former of which has inhibition on renin [21], while the effect of the latter on renin remains undetermined.

As computers are widely being used in aiding the design of drugs, the three-dimensional structure of proteins is identified, and the data of the structure of receptors are being accumulated, which promotes the development of molecular docking [22]. With molecular docking and dynamic simulation being the proven methods for the design of drugs, especially based on the three-dimensional structure of receptors, the interaction between the receptor and the ligand [23] and between the small macromolecular protein receptor and the molecular ligand can be assessed through the study of the key residues of amino acids, interaction sites, and free binding energy in the docking [24]. The paper investigated the interactions of chikusetsusaponin IV and momordin IIc with renin through molecular docking and dynamic simulation.

2. Materials and Methods

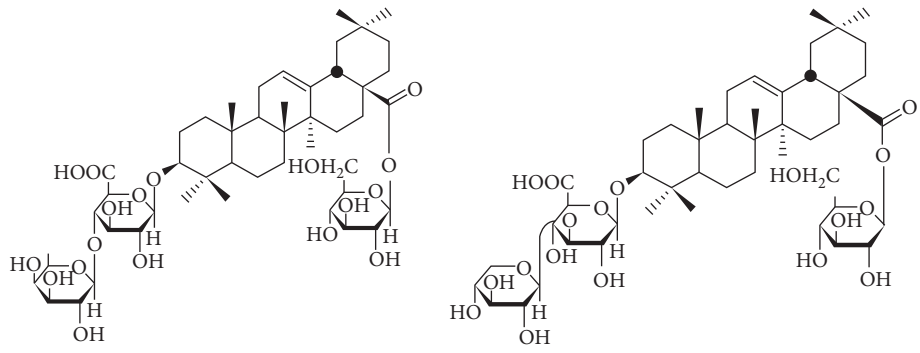
2.1. The Structures of Renin and Saponins. The crystal structure with PDB ID 3OOT was retrieved from the Protein Data Bank (PDB) (http://www.rcsb.org/pdb/), and the ligand $C_8H_{15}NO_6$ was stripped out, using DS (Discovery Studio 3.0), to obtain the three-dimensional structure of renin. The three-dimensional structures of chikusetsusaponin IV and momordin IIc are drawn using PyMol [25] (http://pymol.org), as shown in Figure 1. Then the structures are charged on PRODRG (http://davapc1.bioch.dundee.ac.uk/cgi-bin/prodrg) and optimized for future treatment [26].

2.2. The Molecular Dockings of Renin and Saponins. The water molecules were removed first before the docking which was added the CHARMm force of Discovery Studio 3.0 (DS) for the combination of renin and the saponins. With the Thr85 residue of renin being the active center and a radius of 13 Å being the docking region, the Libdock was performed and its parameters are as follows: number of hotspots: 100; docking tolerance: 0.25; conformation method: FAST; parallel processing: false; docking preference: high quality.

Then, the molecular dockings were started, each producing a structure which was to be gathered using Libdock. The best-combined structures were chosen to obtain intermolecular interaction network using LigPlot+ [26]. The residues of amino acids that have hydrogen bonding and hydrophobic effect were analyzed and corresponded to the active pockets of renin by using DS. Finally, the spatial interaction between the pockets and the saponins was analyzed, considering the free binding energy.

2.3. The Molecular Dynamics Simulation of Docking Complexes. The dynamic simulation was carried out using GROMACS 4.0 [27]. In this experiment, it is the GROMOS 96 force field that was added to the docking complexes. In addition, the temperature was set to 300 K because a water model was added to the system for the solvation effect. Before the simulation, the spatial structures of the docked complexes were optimized twice, one being a 1000-step steepest descent and the other a 2000-step conjugate gradient. During the simulation, the solute molecules were stabilized within 100 ps while the temperature increased gradually from 0 K to 300 K. Then, they were stabilized within 5 ns after the restraint was released. In addition, the real-time structures were observed using VMD. Moreover, the integration step was set to 2 fs and the cutoff of the nonbond interaction 1.2 nm.

In order to reduce the errors caused by the vacuum environment, a certain amount of water was added to the spatial structure of renin using GROMACS and the capacity of the water box was defined by editconf in GROMACS, which was then run and water was added by the genbox command. In the system, the total number of charges was automatically calculated by GROMACS which applied the charges in the metal ion balance system to perform molecular dynamic simulations in a charge-balanced environment [28, 29]. Then, the systems were optimized twice with a 1000-step steepest descent and the other a 2000-step conjugate gradient, with and without the solutes being sterilized. Finally, the free binding energy in the system was calculated after the system was minimized using grompp and marum in GROMACS [30].



(a) (b)

Figure 1: The structures of the saponins. (a) Chikusetsusaponin IV. (b) Momordin IIc.

2.4. The Calculation of Free Binding Energies of the Complexes. The calculation of the free binding energies in the interaction between the ligand and protein is the core issue to test the molecular docking. Using MM-PBSA, the free binding energies can be calculated after the solute molecules are removed in the regular dynamic simulation to obtain the structures that change with the passage of time [31, 32]. The calculation was defined in an attempt to obtain the contribution of each energy so as to have a better analysis of the interaction between renin and the saponins [33]. The equation is as follows:

$$\Delta G_{\text{bind}} = \Delta E_{\text{elec}} + \Delta E_{\text{vdW}} + \Delta G_{\text{pb}} + \Delta G_{\text{sur}}, \quad (1)$$

where ΔG_{bind} is the total free binding energy of the complexes; ΔE_{elec} is the electrostatic interaction; ΔE_{vdW} is the van der Waals interaction; ΔG_{pb} is the polar solvation energy; and ΔG_{sur} is the nonpolar solvation energy.

3. Results and Analysis

3.1. The Molecular Docking. The hydrogen bonding and hydrophobic effects can be calculated using HBPLUS of LigPlot+, a computational program for a statistical analysis of the interaction between receptors and ligands [34, 35]. A floor plan of the amino acids and hydrogen bonds in the interaction can prevent the overlapping and intersection of the bonds. The best docking structure was chosen to obtain the network of the interaction and calculate the amino acid residues because of the hydrogen bonding and hydrophobic effects so as to analyze the spatial forces of the complexes.

In the study, the complexes derived from the docking of the renin and saponins were uploaded in LigPlot+. The hydrogen bonding between momordin IIc and renin was stronger than that between chikusetsusaponin IV and renin, as shown in Table 1. A comparison of the residues of the amino acids in renin that interacted with the saponins showed that Ser230, Tyr85, and Tyr201 formed stable hydrogen bonds.

3.2. The Hydrogen Bonding of the Active Pockets in Renin. Renin is a highly selective aspartic protease with a diploblastic structure. There are active sites of renin in the fissures on each leaf such as $S3^{sp}$, S3, S2, S2′, S1, and S1′ [36]. After the docking, the amino acid residues in the interaction between renin and the saponins in the pockets were calculated , as shown in Figure 2.

Based on the analysis of the hydrogen bonding in the pockets as shown in Table 2, it was found out that the bonding between chikusetsusaponin IV and renin took place in all pockets except for S1 and S2 while the bonding between momordin IIc and renin in all pockets except for S1, which proved that the hydrogen bonding between momordin IIc and renin is stronger, verified in Section 2.1.

An analysis of the varieties of the amino acids in the active renin pockets showed that Ser230 interacts with chikusetsusaponin IV and momordin IIc in $S3^{sp}$ and S2, and Thr85 formed hydrogen bonds with both of the saponins in S3 and Trp201 in S2′.

Therefore, it can be concluded that renin mainly interacts with chikusetsusaponin IV in $S3^{sp}$, S3, and S2′ and with momordin IIc in $S3^{sp}$, S3, S2, and S2′, with $S3^{sp}$, S3, and S2′ being the active pockets. Moreover, Ser230, Tyr85, and Tyr201 are of primary importance for the formation of hydrogen bonds.

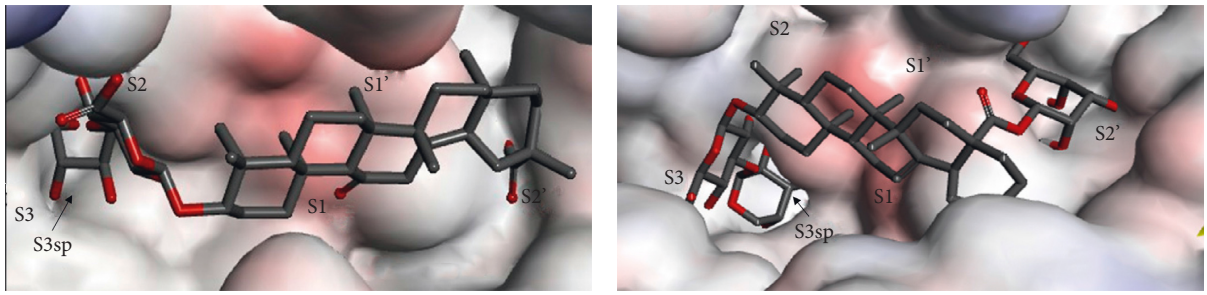
3.3. The Hydrogen Bonding and Hydrophobic Interaction in the Active Pockets in Renin. Analysis of the active pockets where the residues of amino acids existed showed that there were relatively strong hydrophobic interactions in $S3^{sp}$, S3, S2, S1, S1′, and S2′, as shown in Table 3.

Gly228 and Val36 formed a hydrophobic interaction with the saponins in $S3^{sp}$, Ala229 and Gln19 in S3, Met303 in S2, Gln135, Ser41, and Ile137 in S2′, Asp38 and Arg82 in S1, and Tyr83 in S1′. During the interaction, momordin IIc has one more Thr18, Gly40, and Asp226 than chikusetsusaponin IV in S3, S2′, and S1′. Therefore, it can be anticipated that momordin IIc inhibits the hydrophobic interaction more than chikusetsusaponin IV.

3.4. The Stability of Dynamic Trajectory. Root mean square deviation (RMSD) is an important indicator of whether the system has reached a steady state. In order to make sure whether the sampling of the simulations and the free binding energies are correct, the RMSD of the structures of the

Table 1: The hydrogen bonds in the complexes.

	Hydrogen bonds	Ligand atoms	Receptor atoms	Distance (Å)
Chikusetsusaponin IV	1	O78	Trp201-N	3.07
	2	O26	Thr85-OG1	2.88
	3	O48	Ser230-OG	2.68
Momordin IIc	1	O48	Tyr20-N	3.32
	2	O58	Tyr20-N	2.62
	3	O37	Ser230-N	2.37
	4	O36	Thr85-OG1	2.92
	5	O26	Thr85-OG1	2.49
	6	O4	Ser42-OH	2.57
	7	O2	Phe132-N	2.48
	8	O1	Trp201-N	2.89



(a) (b)

Figure 2: Docking in the active pockets in renin. (a) Chikusetsusaponin IV. (b) Momordin IIc.

Table 2: Residues of amino acids with hydrogen bonding in the active pockets.

Saponin	$S3^{sp}$	S3	S2	S2′	S1
Chikusetsusaponin IV	Ser230	Thr85	—	Trp201	—
Momordin IIc	Tyr20	Thr85	Ser230	Ser42, Trp201, Phe132	—

Table 3: Residues of amino acids with hydrophobic interactions in the active pockets of renin.

Saponin	$S3^{sp}$	S3	S2	S2′	S1	S1′
Chikusetsusaponin IV	Val36, Gly228	Ala229, Gln19,	Met303	Gln135, Ser41, Ile137	Asp38, Arg82	Tyr83
Momordin IIc	Val36, Gly228	Ala229, Gln19, Thr18	Met303	Gly40, Gln135, Ser41, Ile137	Asp38, Arg82	Asp226, Tyr83

complexes and the root mean square fluctuations (RMSF) of the residues were calculated.

RMSF was used to determine the relatively flexible and stable areas in the simulation. In addition, the complexes existed in the active areas with low RMSF such as Thr39-Trp45, Met107-Thr112, Leu2224-Ser235, and Ala314-Thr318 where the renin and the saponins interacted. The RMSFs of the residues of amino acids were calculated, as shown in Figure 3, in order to describe the fluctuations of the complexes. As shown in Figure 4, RMSFs generally had large values, meaning that the molecular structure of renin had great flexibility.

The simulation went for 5000 ps and the RMSDs were obtained with the passage of time and compared to the initial frame. The dynamics reached equilibration with average RMSD of 0.2224 nm and 0.2169 nm because there were a few fluctuations after 3000 ps, as shown in Figure 4 and Table 4, proving it was reasonable to analyze the structures of the free binding energies.

3.5. The Calculation of the Free Binding Energy. The free binding energies were calculated using formula (1), as shown in Table 5. Both of the energies are below zero, with the one in the interaction between momordin IIc and renin being −39.0587 kcal/mol and the other −1.10812 kcal/mol, which indicated that both of the saponins have inhibitory effect on renin.

Although having similar van der Waals energy, polar solvation energy, and a nonpolar solvent with momordin IIc, chikusetsusaponin IV has much larger electrostatic energy which is −50.3008 kcal/mol, leading to less inhibitory effect.

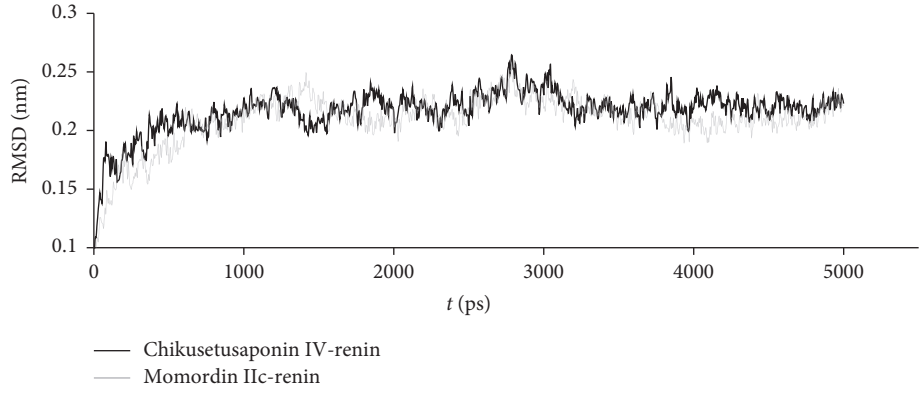


Figure 3: The RMSDs of complexes.

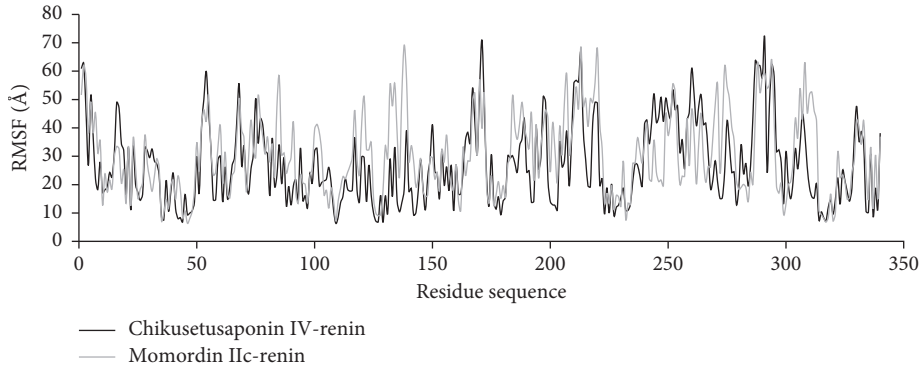


Figure 4: The RMSFs of complexes.

Table 4: The RMSDs of complexes after 3000 ps.

Complexes	RMSD average (nm)	Fluctuation range (nm)
Chikusetsusaponin IV-renin	0.2224	0.068
Momordin IIc-renin	0.2169	0.068

Table 5: Free binding energies of the complexes.

Complexes	ΔE_{vdw}	ΔE_{elec}	ΔG_{pb}	ΔG_{sur}	ΔG_{bind} (kcal/mol)
Chikusetsusaponin IV-renin	−94.587	−50.3008	153.2202	−9.44048	−1.10812
Momordin IIc-renin	−91.6879	−92.2665	154.1899	−9.29422	−39.0587

This proved the correctness of what was mentioned in Section 3.3.

4. Conclusions

In the study, chikusetsusaponin IV and momordin IIc were docked with renin. Based on the scoring of the results by Libdock, it was concluded that the overlapping is relatively good. The analysis of the hydrogen bonding of renin with the saponins showed that the residues of amino acids such as Ser230, Tyr85, and Tyr201 formed the hydrogen bonds, with $S3^{sp}$, S3, and $S2'$ being the active pockets. In addition, the analysis of hydrophobic interactions of renin with the saponins indicated that there are relatively strong hydrophobic interactions of the former with the latter in $S3^{sp}$, S3, S2, S1, $S1'$, and $S2'$, with Gly228, Val36, Ala229, Gln19, Met303, Gln135, Ser41, Ile137, Asp38, Arg82, and Tyr83 being the key amino acids. The dynamic simulation of the complexes revealed that the residues of the amino acids in renin that has strong hydrogen bonding with the saponins have low RMSF and the dynamics of the complexes reaches equilibration after about 1000 ps simulation with average root-mean-square deviations of 0.222 nm and 0.217 nm, respectively. In addition, the complexes existed in the active areas with low RMSF such as Thr39-Trp45, Met107-Thr112, Leu2224-Ser235, and Ala314-Thr318 where the renin and the saponins interacted.

The calculation of the free binding energies of chikusetsusaponin IV and momordin IIc with renin, which

were primarily contributed by electrostatic and van der Waals interaction energies, through MM-PBSA yielded −1.10812 kcal/mol and −39.0587 kcal/mol, respectively, further confirming that momordin IIc has stronger hydrogen bonding and hydrophobic effect in the inhibition of renin than chikusetsusaponin IV. In conclusion, the study proves the significance of further research on the structures and the catalytic mechanism of the saponins in the inhibition of renin.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflicts of interest regarding the content and implications of this manuscript.

Acknowledgments

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