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Comprehensive *In Silico* Analysis of Christinin Molecular Behaviour from *Ziziphus spina-christi* Leaves on *Propionibacterium acnes*

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ABSTRACT

The role of *in silico* studies in the discovery of new drugs is very important and interesting in the recent years, where the results can be used as confirmation of the results of *in vitro* tests carried out experimentally in the laboratory. One of the herbal ingredients is *Ziziphus spina-christi* leaves with effective antibacterial activity, such as for acne-causing bacteria, namely *Propionibacterium acnes*. This is because it contains main secondary metabolites with saponins as the major components which contain christinin as its active compound. There are four known types of christinin, namely christinin-A, christinin-B, christinin-C, and christinin-D. In this study, the molecular interaction of the christinin compound was tested to predict its affinity for *Propionibacterium acnes* compared to clindamycin, as well as to determine the level of safety on the skin so that it can be applied as a topical anti-acne dosage form. *In silico* studies, including molecular docking and toxicity prediction, were used to assess the activity of four molecules of the christinin compound on c-Jun N-terminal kinase (JNK) macromolecules. The christinin molecules form a strong and stable molecular interaction with the active site of the binding of c-Jun N-terminal kinase (JNK) macromolecules. Interestingly, the christinin compound molecules also has a fairly good level of safety based on the three identified parameters. Based on this results christinin compound molecules has potential to be developed as c-Jun N-terminal kinase (JNK) inhibitors candidate to control of skin infections caused by *Propionibacterium acnes* which has potential as a topical anti-acne.

Keywords: *Ziziphus spina-christi leaves; christinin; Propionibacterium acnes; in silico study; anti-acne topical.*

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INTRODUCTION

The role of *in silico* studies in the discovery of new drugs is very important and interesting nowadays, because it is relatively cheaper, effective, fast and precise with a high degree of accuracy. The results of *in silico* studies are usually used as confirmation of the results of *in vitro* tests carried out using experimental microbiological testing methods in the laboratory (Audagnotto & Dal Peraro, 2017; Ozerov et al., 2016). One of its applications is the discovery of herbal medicinal candidates for acne. Acne is a skin health disorder due to increased production of excess oil in the polysebaceous glands which triggers the growth of acne-causing bacteria, namely *Propionibacterium acnes* (Zaenglein et al., 2016). There are many acne treatment options, the most popular of which uses an antibiotic such as clindamycin which is known to cause skin irritation and resistance side effects. Therefore, the use of other effective alternatives therapy such as herbal medication is necessary.

One of the herbal ingredients that can be used to treat acne prone skin is *Ziziphus spina-christi* (L.), Willd (Rhamnaceae). This is evidenced in research which is characterized by the presence of an inhibition zone in the growth media for *Propionibacterium acnes* and *Staphylococcus epidermidis* from the ethanol extract of *Ziziphus spina-christi* leaves (Haeria & Hermawati. et, 2016). It is known that secondary metabolite compounds in the extract of *Ziziphus spina-christi* leaves that can inhibit the growth of microorganisms are alkaloids, flavonoids, polyphenols, tannins and saponins (Asgarpanah, 2012). In addition, *Ziziphus spina-christi* leaves also have anti-inflammatory properties that can treat inflammation and rashes in mild to moderate acne vulgaris (Alzahrani et al., 2019).

In research that utilizes natural flavonoid compounds in *Ziziphus spina-christi* leaves, it is proven to have antioxidant, anti-inflammatory and antibacterial activity which are effective in the treatment of acne. As a result, *Ziziphus spina-christi* with flavonoid components and antioxidant properties in combination with clindamycin 1% is likely to have been more successful in this pathway on reducing acne lesions than standard treatment alone (Shakiba et al., 2019). From the isolated n-butanol extract of *Ziziphus spina-christi* leaves, there are four triterpenoidal saponin glycosides which are named christinin-A, christinin-B, christinin-C, and christinin-D. Christinin-A is the main saponin with a steroide core

structure (Hussein Mahran et al., 1996; Niamat et al., 2012). In this study, the molecular interaction of the christinin compound contained in *Ziziphus spina-christi* leaves was tested to predict its affinity for *Propionibacterium acnes* compared to clindamycin *in silico*, as well as to determine the level of safety on the skin so that it can be applied as a topical anti-acne dosage form.

METHODS

Preparation of the c-Jun N-terminal Kinase (JNK) Macromolecules

In this research, the macromolecule used was the c-Jun N-terminal kinase (JNK) downloaded from Protein Data Bank (http://www.rcsb.org/pdb) with PDB ID 3V3V and has a resolution of 2.70 Å (Baek et al., 2013). These macromolecules are used to explain the mechanism of action of the christinin compound molecule because c-Jun N-terminal kinase (JNK) is involved in *Propionibacterium acnes*-induced inflammation (Cheon et al., 2019). The macromolecules c-Jun N-terminal kinase (JNK) are then prepared by removing water molecules and quercetagetin as native ligands, adding polar hydrogen atoms, and calculating Kollman's partial charge (Fakih, 2020).

Preparation of the Christinin Molecules

In this research, the molecules used are the christinin-A, christinin-B, christinin-C, and christinin-D which were derived from Arabian bidara leaves and have been modelled and optimized using GaussView 5.0.8 and Gaussian09 (Figure 1). The chosen method at this optimizing stage is the semi-empirical method based on the AM1 basis set. The christinin compound molecules which have been modeled and its partial charge data modified is used as input for the molecular docking simulations (Ng et al., 2018).

The Validation of Molecular Docking Methods

In this research, before the molecular docking simulations between the christinin compound molecules and the c-Jun N-terminal kinase (JNK) macromolecules are demonstrated, the method validation must first be performed using MGLTools 1.5.6 with AutoDock 4.2 to determine several parameters to be used in the molecular docking simulations. The method validation of the molecular docking parameters was carried out using the re-docking method. In this re-docking process, the value of Root Mean Square Deviation (RMSD) is limited to a maximum radius of 2 Å (Granchi et al., 2015).

The Simulations of Molecular Docking Approaches

In this research, MGLTools 1.5.6 with AutoDock 4.2 was used to simulate molecular docking. The christinin-A, christinin-B, christinin-C, and christinin-D molecules

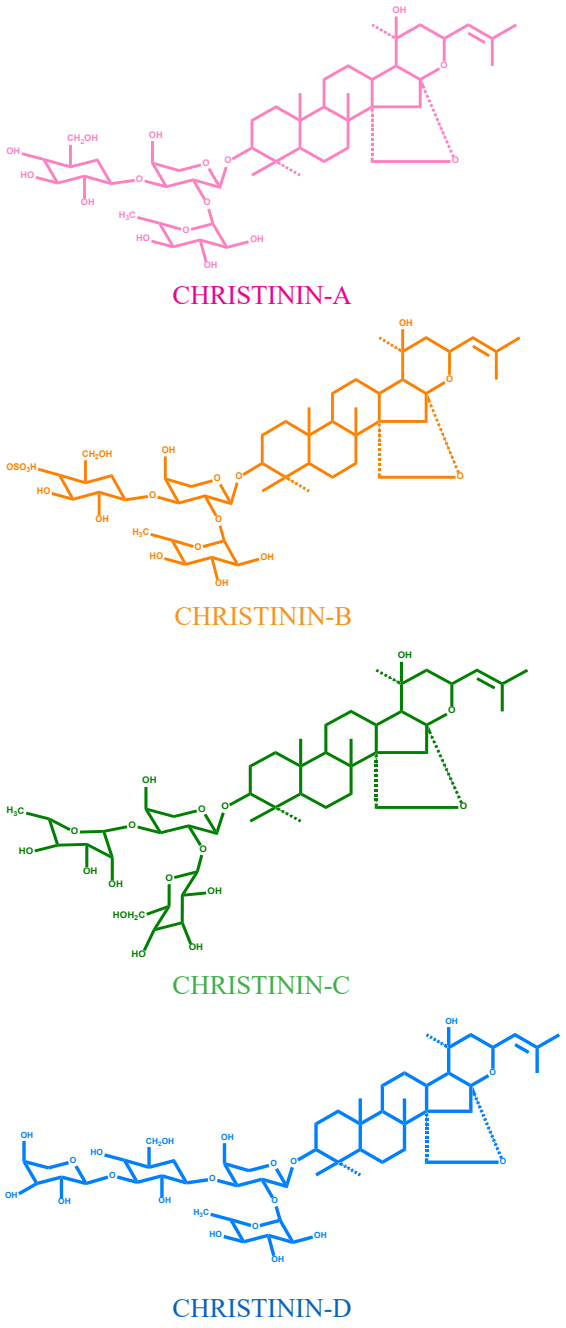

Figure 1. The molecular structure of the Christinin derivatives used in this research

for docking simulations are modelled, optimized, and polar hydrogen atoms are added using the semi-empirical method. The distance between the surface area of the c-Jun N-terminal kinase (JNK) macromolecules and the christinin compound molecules is limited by a maximum radius limit of 0.375 Å. The shape of the Connolly point surface of the molecule into different components including convex, concave, and flat patch is produced through the AutoDock algorithm (Gaillard, 2018). All simulations were performed using a grid box size of 94 x

90 x 90 and the Lamarckian Genetic Algorithm method with 100 conformations. It also changes the orientation of the molecule relative by limiting flexibility in the side chains of the interacting surface and allowing the movement of small and rigid objects (Fakih & Dewi, 2020).

The Evaluation of Molecular Docking Results

In this research, the results obtained from the molecular docking simulation were then identified, evaluated, and explored the molecular interactions formed between the c-Jun N-terminal kinase (JNK) macromolecules and the christinin compound molecules based on the value of the binding free energy (Ferreira et al., 2015). The amino acid residues that play a role in the molecular interactions formed were then observed using the BIOVIA Discovery Studio 2020 (Khaerunnisa et al., 2020).

The Dynamical Interactions of Molecular Stability

Molecular dynamics simulations were demonstrated using the Gromacs 2016.3 with an AMBER99SB-ILDN force field (Smith et al., 2015). Topological ligands parameterization was made using AnteChamber PYthon Parser interfacE (ACPYPE) (Sousa Da Silva & Vranken, 2012). The electrostatic force at the distance was determined by the Particle Mesh Ewald method. Neutralization of the system is accomplished by adding Na^+ and Cl^- ions. The solution is done using the TIP3P water cube model. The preparation stage for the simulation includes the minimization stage, heating up to 310 ^{0}K, temperature equilibrium, pressure equilibrium, and followed by the simulation process. Moreover, 20 ns of MD production was carried out at a time step of 2 fs. At the end of the simulation, analysis of the root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg), and the solvent-accessible surface area (SASA) was carried out (Yamagishi et al., 2014).

The Calculations of MM/PBSA Binding-Free Energy

The molecular mechanics Poisson–Boltzmann surface area (MM/PBSA) calculations were performed using the g_mmpbsa a package that is integrated with the Gromacs 2016.3. According to the MM-PBSA method, the binding free energy of the complex is the difference between the free energies of the complex and the unbound receptor and the free ligand. The polar desolvation energy is calculated based on the Poisson-Boltzmann equation with a grid size of 0.5 Å. The dielectric constant of the solvent is set at 80 to represent water as the solvent. The calculation of the nonpolar contribution is done by calculating the surface area accessed by the solvent with a solvent radius of 1.4 Å. The calculation of the receptor-ligand binding-free energy is demonstrated based on the simulation results of complex molecular dynamics (Ren et al., 2020).

The Prediction of Molecular Toxicity

In this research, toxicity prediction was performed on all christinin compound molecules using Toxtree v.3.1.0 (Muttaqin et al., 2017). There are three parameters used in predicting toxicity, namely Skin Irritation/Corrosion, Eye Irritation and Corrosion, and Skin Sensitisation Reactivity Domains. Skin Irritation/Corrosion is a parameter that can assess a compound molecule whether it can potentially cause irritation or corrosion or a combination of the two. Eye Irritation and Corrosion are needed to assess whether it can potentially cause irritation or corrosion to the eyes. Then Skin Sensitisation Reactivity Domains to assess the sensitivity of compound molecules in the skin area (Hirota et al., 2018).

RESULTS AND DISCUSSION

The Binding Modes of Molecular Docking Approaches

The christinin-A, christinin-B, christinin-C, and christinin-D molecules derived from *Ziziphus spina-christi* leaves that have been modeled and optimized with a GaussView 5.0.8 and Gaussian09 are then identified, evaluated, and explorated for their affinity and interaction with the c-Jun N-terminal kinase (JNK) *Propionibacterium acnes*-induced inflammation that have been prepared through molecular docking simulations using the AutoDock algorithm. Prior to the simulation, the docking method was validated for Quercetagetin as native ligands. The RMSD value obtained from the docking method validation showed 0.78 Å. Thus, the parameters of the docking method validation results can be used in the molecular docking simulation stage in the form of a grid box size of 94 x 90 x 90 and a grid center of 30.614 x 44.085 x 4.212.

The results of molecular docking simulations in Table 1 show that the christinin-A has the best affinity with the active binding site c-Jun N-terminal kinase (JNK) compared to the other christinin compound molecules and clindamycin as a positive control, with an binding free energy values of −7.89 kcal/mol (christinin-A), −5.73 kcal/mol (christinin-B), −5.98 kcal/mol (christinin-C), −7.07 kcal/mol (christinin-D), and −7.31 kcal/mol (clindamycin), respectively. These results indicate an

Table 1. The affinity of the christinin derivatives against the c-Jun N-terminal kinase (JNK)

Compound molecule	Binding free energy (kcal/mol)
Quercetagetin	−9.25
Clindamycin	−7.31
Christinin-A	−7.89
Christinin-B	−5.73
Christinin-C	−5.98
Christinin-D	−7.07

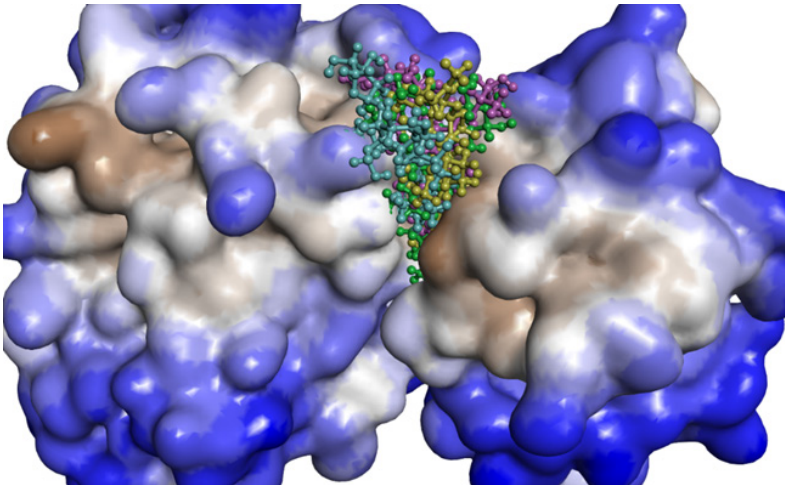

Figure 2. The binding modes of christinin-A (red), christinin-B (yellow), christinin-C (green), and christinin-D (blue) in the binding site area of the c-Jun N-terminal kinase (JNK) macromolecules

Table 2. The interactions between Christinin derivatives against c-Jun N-terminal kinase (JNK) macromolecules

Compound molecule	Number of interactions	Amino acid residues
Quercetagetin	16	Lys55, Met111, Asn114, Asp169, Met111, Glu73, Leu110, Val158, Leu168, Met108, Ala53, Val158, Leu168, Val40, Lys55, Met108
Clindamycin	11	Asn114, Asn114, Asp112, Met111, Asp169, Ser155, Val40, Leu110, Leu168, Met108, Leu168
Christinin-A	24	Asn51, Asp112, Asp112, Ser161, Asp112, Asp112, Ile32, Ile32, Ile32, Val40, Leu110, Ala113, Val158, Val158, Leu168, Val158, Leu110, Ile32, Leu110, Val40, Met108, Met108, Leu168, Leu110
Christinin-B	18	Pro31, Ile32, Ile32, Ile32, Val40, Ala113, Val158, Val158, Leu168, Val158, Leu110, Ile32, Leu110, Val40, Met108, Met108, Leu168, Ile32
Christinin-C	17	Ser155, Asp112, Ile32, Ile32, Ile32, Ala113, Val158, Val158, Leu168, Val158, Leu110, Ile32, Leu110, Met108, Leu168, Met108, Leu168
Christinin-D	18	Glu109, Pro31, Pro31, Ile32, Ile32, Ile32, Ala113, Val158, Ile32, Ile32, Val40, Val158, Ile32, Val40, Leu168, Val40, Lys55, Lys30

Information : ■ Hydrogen Bond, ■ Hydrophobic Interaction

affinity that is not better than Quercetagetin as native ligands, however the whole molecule of the christinin and clindamycin compounds has conformational similarities when interacting with the active site of c-Jun N-terminal kinase (JNK). This phenomenon predicted that there is a promising sign of the christinin-A as an inhibitor of c-Jun N-terminal kinase (JNK) because it has strong and stable binds and interactions in the active site area of the target macromolecule (Fakih et al., 2020).

Based on the results of visualization of molecular docking simulations, christinin-A, christinin-B, christinin-C, and christinin-D showed conformational molecular interactions that were similar to the Quercetagetin as native ligands of the c-Jun N-terminal kinase (JNK) and positive controls. However, the whole christinin molecule was able to occupy a patch with a relatively high degree of polarity at the active binding site of the macromolecular c-Jun N-terminal kinase (JNK) (Figure 2). This phenomenon can occur because the AutoDock algorithm supports the christinin compound molecules to move freely without rigid bonds with the molecular docking system used (Alogheli et al., 2017). Overall, the interactions formed by christinin-A outnumber

other christinin and clindamycin compounds, with 24 interactions including six hydrogen bonds (with Asn51, Asp112, and Ser161), and eighteen hydrophobic interactions (with Pro108, Pro132, Val202, Met235, Pro241, His246, Ile249, Pro293, Phe294, and Val297) (Table 2).

In general, the christinin compound molecules have the same interaction on several amino acid residues, such as with Val40, Ala53, Lys55, Met108, Leu110, Met111, Asn114, Val158, Leu168, Asp169, and Myu401. This indicates that the area is very potential as a place to attach inhibitory molecules suitable for c-Jun N-terminal kinase (JNK) macromolecules, especially compounds with large molecular weight. Unlike the case with the Quercetagetin as native ligands active binding site which can only be occupied by small molecular compounds, such as clindamycin. This phenomenon is predicted by the ability of clindamycin which is only able to form eleven interactions with c-Jun N-terminal kinase (JNK) macromolecules. Then interestingly, the christinin compound molecule has more molecular interactions compared to Quercetagetin as native ligands at the active binding site of target macromolecules (Elokely & Doerksen, 2013).

The most responsible interaction of ligand-protein complexes is hydrogen bonding, especially the christinin compound molecule which acts as a hydrogen bond donor and amino acid residues on the target macromolecule as hydrogen bond acceptors. Most of the hydrogen bonds between the christinin compound molecule and the c-Jun N-terminal kinase (JNK) macromolecules are relatively strong, with average bond lengths ranging from 3 Å (Dar & Mir, 2017). Apart from hydrogen bonding, there are also contributions from hydrophobic interactions. It can be predicted that hydrogen bonding and hydrophobic interactions play an important role in stabilizing ligand-protein complexes during molecular docking simulations.

The Stability Assessment of Molecular Dynamics Interactions

The purpose of this molecular dynamics simulation is to identify the stability of the interaction of each complex system for 20ns using the initial conformation of molecular docking results. Based on the snapshot taken at the beginning of the simulation (in white), 5ns, 10ns, 15ns, and at the end of the simulation, it can be observed that the conformational changes of each christinin compound generally occur when the simulation has reached 5ns (Figure 3). The position of the four compounds changed during the simulation, however a significant change was shown by the christinin-D compound. The compound moved flucatively and began to move away from the active site area of c-Jun N-terminal kinase (JNK) macromolecules.

The dynamically of interactions between the christinin compound and its target macromolecules were studied using molecular dynamics simulations using explicit solvents. Strong affinity tends to reduce the movement of the bonded atom and will generally stabilize the binding site region of the c-Jun N-terminal kinase (JNK). This phenomenon can be analyzed by calculating the RMSD value of the target macromolecular binding site during the 20ns simulation to ensure stability and rationality of the selected conformation. The RMSD graph in Figure 4 shows that the native ligand and christinin-D compounds fluctuate during the molecular dynamics simulation, with the average RMSD value of each compound, 2.80 Å (native ligand) and 2.82 Å (christinin-D).

Identification of the RMSF value based on the amino acid residues found at the active site of the target macromolecule is needed to support the stability data of the RMSD value. The whole complex system in general has the ability to bind firmly to amino acid residues in the macromolecular binding area of the c-Jun N-terminal kinase (JNK). Some of these amino acid residues include Val40, Ala53, Lys55, Met108, Leu110, Met111, Asn114,

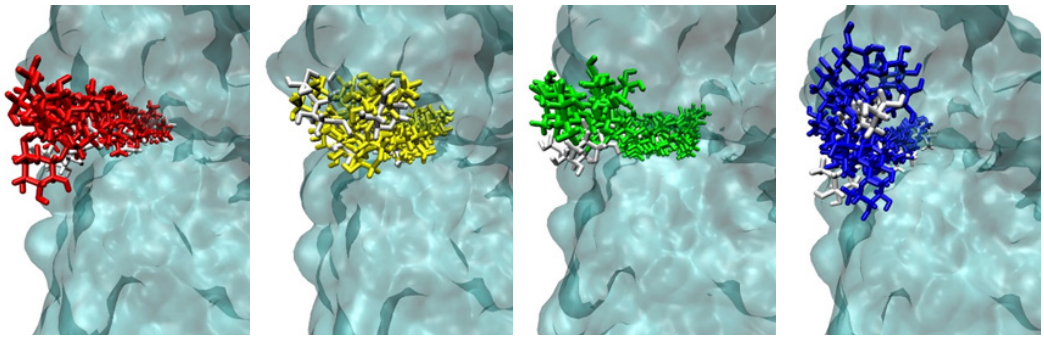

Figure 3. The conformation changes of christinin-A (red), christinin-B (yellow), christinin-C (green), and christinin-D (blue) during molecular dynamics simulations

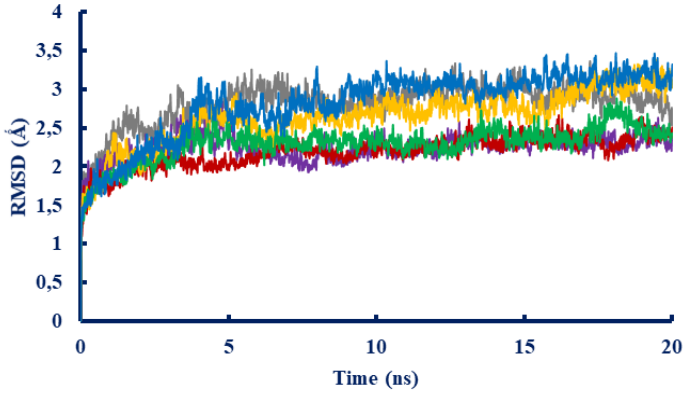

Figure 4. RMSD graph of the complex system from native ligand (gray), Clindamycin (purple), Christinin-A (red), Christinin-B (yellow), Christinin-C (green), and Christinin-D (blue)

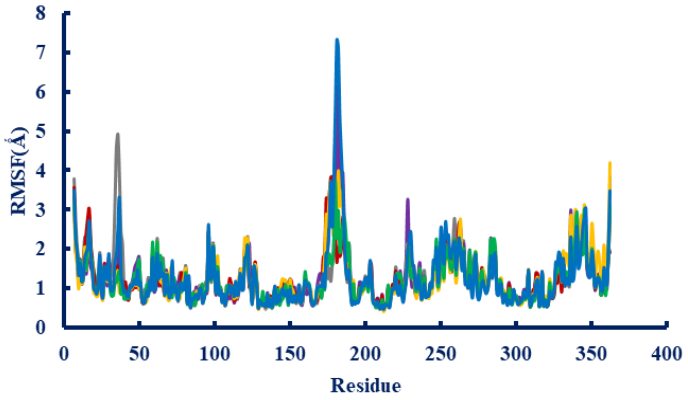

Figure 5. RMSF graph of the complex system from native ligand (gray), Clindamycin (purple), Christinin-A (red), Christinin-B (yellow), Christinin-C (green), and Christinin-D (blue)

Val158, Leu168, and Asp169. The graph in Figure 5 shows that there are similarities in the results with the RMSD graph, the average RMSF value of the native ligand shows instability during the simulation, with an average value of 1.30 Å.

Furthermore, measurements are made of the radius gyration values to determine the stability of the complex, whether a complex system is stable in folded or unfolded form during molecular dynamics simulations showing less compactness (more revealed) of the receptor-ligand complex. In addition, identification of the solvent-accessible surface area (SASA) is also carried out to predict the extent to which the c-Jun N-terminal kinase (JNK) macromolecules undergo conformational changes during the simulation which can be accessed by water molecules (Petrov & Zagrovic, 2014).

The value of the radius of gyration shows that there is no significant difference from the whole complex system. Nevertheless, the native ligand has a high average Rg value compared to christinin compound and clindamycin, with an average Rg value of 2.25 nm. These results are supported by the SASA analysis which shows that the native ligand has a high value, with a value of 183.82 nm^2. From this analysis of the radius of gyration and SASA, it can be predicted that the christinin compound might act as a more potent inhibitor of c-Jun N-terminal kinase (JNK) macromolecules.

The Affinity Prediction of MM/PBSA Binding-Free Energy Calculation

The final step is to calculate the binding-free energy using the MM/PBSA method for several trajectories selected from the simulation results of molecular dynamics. Based on the results of the MM/PBSA calculations contained in Table 3, it can be observed that christinin-A, christinin-B, and christinin-D have better affinity than native ligand and clindamycin on c-Jun N-terminal kinase (JNK) macromolecules.

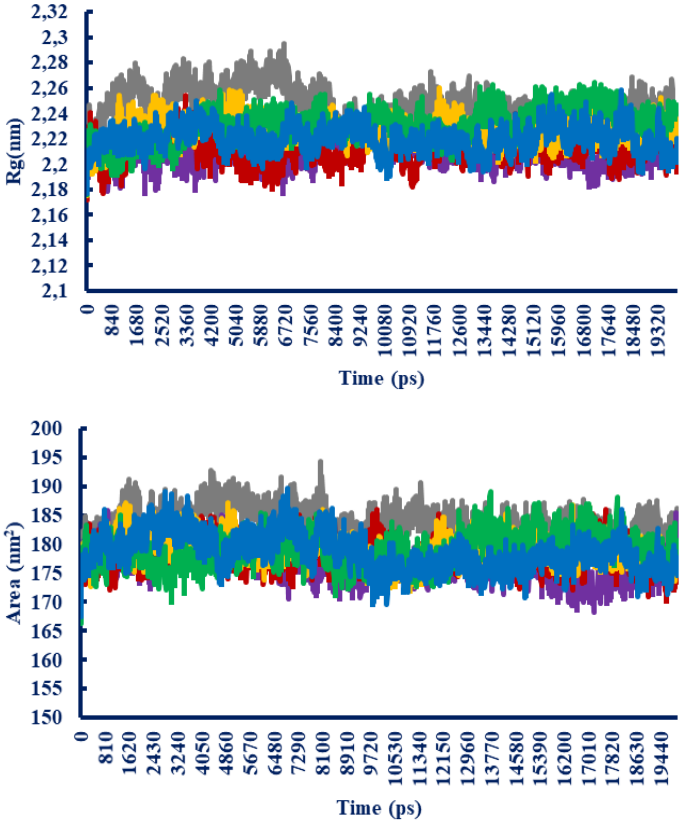

Figure 6. Radius gyration and SASA graphs of the complex system from native ligand (gray), Clindamycin (purple), Christinin-A (red), Christinin-B (yellow), Christinin-C (green), and Christinin-D (blue)

Table 3. Binding-free energy of receptor-ligand interaction dynamics calculated by MM/PBSA methods

Receptor-Ligand Complex	ΔE_{vdw} (kJ/mol)	ΔE_{ele} (kJ/mol)	ΔG_{PB} (kJ/mol)	ΔG_{NP} (kJ/mol)	ΔG_{Bind} (kJ/mol)
Quercetagetin	−184.636	−35.890	145.612	−16.078	−90.992
Clindamycin	−172.331	−49.107	131.974	−18.736	−108.200
Christinin-A	−212.598	−28.369	138.113	−22.508	−125.362
Christinin-B	−234.038	−156.139	176.308	−27.301	−241.170
Christinin-C	−210.388	−21.856	162.332	−23.881	−93.794
Christinin-D	−274.638	−55.233	182.046	−26.319	−174.144

Note : ΔEvdw = van der Waals contribution, ΔEele = electrostatic contribution, ΔGPB = polar contribution of desolvation, ΔGNP = non-polar contribution of desolvation.

The compounds christinin-A, christinin-B, and christinin-D have binding-free energy values of −125.362 kJ/mol, −241.170 kJ/mol, and −174.144 kJ/mol during molecular dynamics simulations. Whereas the christinin-C compound has a binding-free energy value that is not better than clindamycin, with a value of −93.794 kJ/mol. In particular, the energies that contribute the most during the simulation are van der Waals interactions, electrostatic interactions, and non-polar interactions. This phenomenon is because the MM/PBSA approach allows observing the influence of van der Waals and electrostatic contributions as well as changes in receptor-ligand affinity which are influenced by the solvation process of complex systems (Al-Khafaji & Taskin Tok, 2020).

The Toxicity Prediction of Christinin Derivatives

This toxicity test is performed to predict the potential toxicity of christinin derivatives, considering that this compound is a large molecule with a high melting point. In addition, to ensure that there is no potential toxicity when it is formulated in a topical dosage form. Based on research data, the butanol extract of *Zizyphus spina-christi* leaves orally as antidiabetic to rats did

Table 4. The toxicity prediction results of Christinin derivatives

Compound Molecule	Skin Irritation / Skin Corrosion	Eye Irritation and Corrosion	Skin Sensitisation Reactivity Domains
Clindamycin	Unknown	Unknown	Alert for identified
Christinin-A	Not corrosive to skin	No eye irritation	No skin sensitisation reactivity
Christinin-B	Not corrosive to skin	No eye irritation	No skin sensitisation reactivity
Christinin-C	Not corrosive to skin	No eye irritation	No skin sensitisation reactivity
Christinin-D	Not corrosive to skin	No eye irritation	No skin sensitisation reactivity

not show any signs of hepatotoxicity, nephrotoxicity or haematological changes. Results of acute toxicity tests, show that the butanol extract of *Zizyphus spina-christi* leaves is safe, having a relatively high LD50 value in mice (Abdel-Zaher et al., 2005). Also in the dry ethanolic extract of *Ziziphus jujuba* leaves showed low toxicity in the anti-inflammatory potency test on two experimental inflammation models in rat (Hovaneţ et al., 2016). The prediction of the toxicity test was carried out using Toxtree v.3.1.0. Toxtree v.3.1.0 has many test parameters with different toxicity test results. The molecular toxicity test of the christinin compound was demonstrated using three test parameters, including Skin Irritation/Corrosion, Eye Irritation and Corrosion, and Skin Sensitisation Reactivity Domains. Skin Irritation/ Corrosion is a parameter that can assess whether a chemical has the potential to cause irritation or corrosion or a combination of both. If a chemical has a melting point greater than 200^{o}C, then the compound has no potential to cause irritation or corrosion. Based on the toxicity prediction results in Table 4, it was found that the four molecules of christinin compounds did not have the potential to cause irritation or corrosion. The category of irritation or corrosion here means that a compound does not cause severe burns and does not irritate the skin (Schultz et al., 2015).

Eye irritation and corrosion required physical and chemical data properties such as testing on skin irritation/ corrosion parameters (Zhu et al., 2016). The test results of the christinin compound molecule on this parameter are non-corrosive to the skin and do not cause severe eye burns. Similar to the results of the two previous parameters, christinin-A, christinin-B, christinin-C, and christinin-D did not have high sensitivity to skin based on the Skin Sensitisation Reactivity Domains parameter.

CONCLUSION

The christinin compound molecules can form a strong and stable molecular interaction with the active site of the binding of c-Jun N-terminal kinase (JNK) macromolecules. This phenomenon indicated by the best affinity value compared to the christinin compound molecules against native ligand and clindamycin. Moreover, the christinin compound molecules also have good interaction stability during molecular dynamics simulations, indicated by the values of RMSD, RMSF, the radius of gyration, SASA, and MM/PBSA calculations. Interestingly, the christinin compound molecules also has a fairly good level of safety based on the three identified parameters. Based on the results of this research it was predicted that the christinin compound molecules has the potential as a candidate for c-Jun N-terminal kinase (JNK) macromolecular inhibitors in the control of skin infections caused by *Propionibacterium acnes* which has potential as a topical anti-acne.

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