ABSTRACT

Objective: Study the in silico plasmepsin 1 and plasmepsin 2 inhibition antimalarial effects of roselle (Hibiscus sabdariffa L.) calyces flavonoids compared to artemisinin as astandard compound for antimalarial to inhibit plasmepsin 1 and plasmepsin 2.

Methods: Partition coefficient was predicted by the ChemDraw Ultra. In silico molecular docking was done by Protein-Ligand ANTS System. Visualization was done by Yet Another Scientific Artificial Reality Application. Connector for Windows operation system to Linux operation system was done by Co Pendrive Linux. Three dimensions enzyme structure models used in this research were plasmepsin 1 and plasmepsin 2 with the protein data bank code 3QS1 and 1LEE obtained through the website http://www.rcsb.org/pdb. Two dimensions and three dimensions conformation model of compounds were generated by Marvin Sketch.

Results: Partition coefficient of roselle calyces flavonoids quercetin, gossypetin, hibiscetin, and artemisinin, respectively, were 0.58, –0.44, –0.43, and 3.17. Higher partition coefficient means easier to penetrate into the cell. Docking score of roselle calyces flavonoids quercetin, gossypetin, hibiscetin, and artemisinin to plasmepsin 1, respectively, were −70.1989, −70.9454, −70.5870, and −61.7685 to plasmepsin 2, respectively, were −73.8620, −76.0086, −78.8930, and −61.7437. Lower docking score means a better potential activity to protein enzyme.

Conclusion: Roselle calyces flavonoids (quercetin, gossypetin, and hibiscetin) show the stronger activity than artemisinin to inhibit plasmepsin 1 and plasmepsin 2.

Keywords: In Silico, Hibiscus sabdariffa, Flavonoids, Antimalarial, Plasmepsin 1, Plasmepsin 2.
Table 1: Partition coefficient and docking score of compound with the receptor protein enzyme plasmepsin 1 and plasmepsin 2

<table>
<thead>
<tr>
<th>Number</th>
<th>Compound</th>
<th>Molecular formula</th>
<th>Weight</th>
<th>Partition coefficient</th>
<th>Docking score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Quercetin</td>
<td>C_{15}H_{10}O_{9}</td>
<td>304.25</td>
<td>0.58</td>
<td>-70.1989</td>
</tr>
<tr>
<td>2</td>
<td>Gossypetin</td>
<td>C_{15}H_{10}O_{9}</td>
<td>318.24</td>
<td>-0.44</td>
<td>-70.9454</td>
</tr>
<tr>
<td>3</td>
<td>Hibiscetin</td>
<td>C_{15}H_{10}O_{9}</td>
<td>334.23</td>
<td>-0.43</td>
<td>-70.5870</td>
</tr>
<tr>
<td>4</td>
<td>Artemisinin</td>
<td>C_{15}H_{10}O_{9}</td>
<td>282.33</td>
<td>3.17</td>
<td>-61.7685</td>
</tr>
</tbody>
</table>

Fig. 2: Overlapping between native ligands after redocking and native ligands before redocking ([a] KNI, [b] R36) and interaction between native ligands after redocking to its original binding pockets and protein enzyme ([c] KNI and plasmepsin 1; [d] R36 and plasmepsin 2)

RESULTS AND DISCUSSIONS

The protein enzyme plasmepsin 1 and plasmepsin 2 with code 3QS1 and 1LEE have the native ligand KNI and R36. The native ligands were extracted and redocked into its original binding pockets. The root mean square deviation values resulted from these overlapping between native ligands after redocking to its original binding pockets and native ligands before redocking to its original binding pockets were 1.7099 Å and 1.2918 Å, which was <2.0000 Å, a value typically used in evaluating the success of docking algorithms, indicating the docking methods was valid [17]. Fig. 2 shows the overlapping between native ligands after redocking and native ligands before redocking and interaction between native ligands after redocking to its original binding pockets and protein enzyme.

Prediction of the partition coefficient value of compound is an initial test to predict the solubility of compounds in the water phase and the oil phase. Testing the antimalarial effects of compounds were done by in silico docking between protein enzyme plasmepsin 1 and plasmepsin 2 with roselle calyces flavonoids (hibiscetin, gossypetin, and quercetin) as the test compound and artemisinin as the standard compound resulting the docking score. Table 1 shows the partition coefficient and the docking score of test compound and standard compound with the receptor protein enzyme plasmepsin 1 and plasmepsin 2. Fig. 3 shows the relation graph between compound and docking score results on protein enzyme.

From the partition coefficient data, it can be seen that artemisinin as a standard compound for antimalarial to inhibit plasmepsin 1 and plasmepsin 2 have a higher partition coefficient than roselle calyces flavonoids as the test compound. Higher partition coefficient of artemisinin as a standard compound for antimalarial to inhibit plasmepsin 1 and plasmepsin 2 than quercetin, gossypetin, and hibiscetin means that the solubility of artemisinin as a standard compound for antimalarial to inhibit plasmepsin 1 and plasmepsin 2 in oil phase was higher than quercetin, gossypetin, and hibiscetin. Higher solubility in oil phase of artemisinin as a standard compound for antimalarial to inhibit plasmepsin 1 and plasmepsin 2 was easier than quercetin, gossypetin, and hibiscetin. Partition coefficient only means the ability of the drug to soluble in the oil phase (cell membrane) to penetrate into the cell. The activity of the drug does not only depend on the penetration ability of the drug to penetrate into the cell but also depend on the binding ability of the drug to bind with the binding pocket. The activity of the drug to bind with the binding pocket depends on the structure.

From the docking score data, it can be seen that roselle calyces flavonoids quercetin, gossypetin, and hibiscetin as the test compound...
have lower docking score on molecular docking to plasmepsin 1 and plasmepsin 2 than artemisinin as a standard compound for antimalarial to inhibit plasmepsin 1 and plasmepsin 2. Lower docking score on molecular docking to plasmepsin 1 and plasmepsin 2 of quercetin, gossypetin, and hibiscetin were stronger than artemisinin as a standard compound for antimalarial to inhibit plasmepsin 1 and plasmepsin 2. Lower energy need to penetrate into protein enzyme binding pocket plasmepsin 1 and plasmepsin 2 of quercetin, gossypetin, and hibiscetin were lower than artemisinin as a standard compound for antimalarial to inhibit plasmepsin 1 and plasmepsin 2. Lower energy need to penetrate into protein enzyme binding pocket plasmepsin 1 and plasmepsin 2, easier to penetrate into protein enzyme binding pocket plasmepsin 1 and plasmepsin 2, stronger activity to interact with the protein enzyme plasmepsin 1 and plasmepsin 2 means the energy needed to penetrate into the protein enzyme binding pocket plasmepsin 1 and plasmepsin 2 of quercetin, gossypetin, and hibiscetin were easier than artemisinin as a standard compound for antimalarial to inhibit plasmepsin 1 and plasmepsin 2. Easier ability to penetrate into the protein enzyme binding pocket of quercetin, gossypetin, and hibiscetin than artemisinin as a standard compound for antimalarial to inhibit plasmepsin 1 and plasmepsin 2 means the activity to interact with protein enzyme plasmepsin 1 and plasmepsin 2 of quercetin, gossypetin, and hibiscetin were stronger than artemisinin as a standard compound for antimalarial to inhibit plasmepsin 1 and plasmepsin 2. The docking score represents the binding affinity of the ligand to the enzyme, smaller docking score value shows stronger interaction [18]. Fig. 4 shows the visualization of interaction between compounds and protein enzyme plasmepsin 1 and plasmepsin 2.

Increasing costs of drug development and reduced number of new chemical entities have been a growing concern for new drug development in recent years. Therefore, there is a need for the use of alternative tools to get answers on the efficacy and safety faster, with more certainty and at lower cost. One such alternative tool is the in silico drug design or the computer-aided drug design. In silico drug design can play a significant role in all stages of drug development from the preclinical discovery stage to late stage clinical development [19]. The results obtained in silico screening have shown that it represents the best way to get accurate results in a very short period and saving manner [20]. Although the application of docking and scoring has led to some remarkable successes, there are still some major challenges ahead [21].

CONCLUSIONS

Flavonoids are abundantly contained in roselle calyces can inhibit the plasmepsin 1 and plasmepsin 2. All the roselle calyces flavonoids (quercetin, gossypetin, and hibiscetin) show the lower docking score on molecular docking to plasmepsin 1 and plasmepsin 2, lower energy need to penetrate into protein enzyme binding pocket plasmepsin 1 and plasmepsin 2, easier to penetrate into protein enzyme binding pocket plasmepsin 1 and plasmepsin 2, stronger activity to interact with the protein enzyme plasmepsin 1 and plasmepsin 2 than artemisinin as the standard plasmepsin 1 and plasmepsin 2 inhibition drug.

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