Research Article

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In Silico Molecular Modeling and Docking Studies of Aquaporin-3 with Centella asiatica Active Compound

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Abstract

Aquaporins (AQPs) are keyfactor in the mechanism of skin hidration as water channel. The most abundant AQP present in the skin and more specifically in plasma membrane of epidermal keratinocytes is Aquaporin 3 (AQP3). Centella asiatica was commonly use in wound healing treatment and in anti aging cosmetic, The biologically active ingredients are triterpenes namely asiatic acid, madecassic acid, asiaticoside, and madecassoside. In this study, we developed a computational model using Autodock4 program to predict possible binding sites and binding energies between Centella asiatica active compounds and AQP3. The protein structure of AQP3 were predicted using Modeller software. Ligands structure were downloaded from chEBI database and converted to PDB file using OpenBabel. Prediction of ligand binding sites were done using Q-Site Finder. Docking studies were done in Autodock4 software. Our result suggested that all ligands that we compared were attached on the same binding site at Alanin 234. However, Asiaticossite and Madecassoside had higher mean binding energies. These higher mean binding energies may be caused by some bonds created by glucose-chain of Asiaticoside and Madecassoside

Keywords: Aquaporin, AQP3, Centella asiatica, Triterpenes, Asiatic acid, Madecassic acid, Asiaticoside, Madecassoside, Q-Site Finder, OpenBabel, Autodock4.

Introduction:

Aged skin is manifested by reduced stratum corneum (SC) moisturization, and although transepidermal water loss (TEWL) is know to be normal or improved with age, the epidermal barrier repair capacity after removing the superficial layer of the barrier by tape stripping is significantly impaired (1).

The aquaporins (family of protein) that form channel to facilitate the transport of water across membranes has become of significant interest for its role in epidermal water maintenance (2) Aquaporin-3 (AQP3) has been a particular focus because it is an aquaglycerospore, it can cotransport glycerol, an it's absence result in skin dryness, reduce 3C hydration and elasticity and delayed barrier recovery (2,3,4).

Centella asiatica (Apiceae) has been used as traditional herbal medicine in Malaysia and other part of Asia for hundreds of years. It is

commonly known as pegaga in Malaysia, pennywort and gotu kola in America, and pegagan in Indonesia (5). This tropical plant has been used for various medicinal purposes such as wound healing, treatment of asthma, ulcers, leprosy, lupus erythematosus, psoriasis, vein diseases, for memory improvement, as an antidepressant, antibacterial, antifungal, and anti-cancer agent (6,7). Its also can be used as herbal anti aging cosmetic(6). The major biologically active ingredients are triterpenes namely asiatic acid, madecassic acid, asiaticoside, and madecassoside (7,8).

Computational (in silico) methods have been developed and widely applied in biomolecular and biotechnological field for pharmacology hypothesis development and testing.(9,10). Such methods have seen frequent use in the discovery of novel molecules with affinity to a target, absorption, distibution, metabolism, excretion

as for physicochemical characterization of a new drug.(10,11). For example, a study of molecular docking of compound isolated from fruits of *Helicteres isora* for antidiabetic activity(10). In this study, we developed a computational model using Autodock tools program to predict possible binding sites between *Centella asiatica* active compounds and AQP3.

We performed in silico docking study. Molecular docking is a computational procedure that attempt to predict non-covalent binding of macromolecules or more frequently on macromolecule (receptor) and a small molecule (ligand) efficiency (9,11).

Material And Methods:

Protein Modeling

First of all, Aqp3's protein sequence downloaded from Genebank database. The sequence aligned by Protein BLAST module in Sali Lab's Modeller Software to search the most possible template to make homology modeling. The output (1ldf.pdb) were used as template for homology modeling by the same software. From this process, ten possible protein models were created. We selected the best model by analyzed and compared DOPE assessment score from each model (12).

Ligand Preparations

Asiatic Acid, Madecassic acid, Asiaticoside, and Madecassoside chemical structures downloaded from chEBI database at <http://www.ebi.ac.uk/chebi/>. The downloaded Mol files converted to pdb format by openBabel software to make them readable by the docking program (Autodock4)(13).

Molecular Docking

The best Aqp3 protein model were uploaded to Q-site finder site (<http://www.modelling.leeds.ac.uk/qsitefinder/>) to find the possible ligand binding sites. The result became the area parameter for the later docking process (14).

We used Autodock Tool 1.5.6 to simplified the docking procedure by visualizing the standard Autodock4's text-rich process. First of all, we downloaded Autodock4, AutoGrid4, and mgltools_1.5.6 (Autodock Tool) and installed them to our processing computer. Then, we used Autodock Tool to visualize the docking process of each ligand (Asiatic Acid, Madecassic acid, Asiaticoside, and Madecassoside) in pdb format to the best Aqp3 protein model with Q-site finder's area parameter by Autodock4. From, these docking processes we obtained each ligand binding site and its binding energy (13). The binding site of each ligand were visualized by Py-Mol software and the binding energy compared by table (13,15).

Result and Discussion:

First of all, the protein modeling method were used because the structure of AQP3 were not existed in PDB database. All PDB files we found on various sources on Internet were only predicted versions of AQP3, so, we made our own predicted protein using Modeller which might be the best method available to do homology modeling on transmembrane protein such as AQP3 (12, 16). The software choose 1ldf as the template of AQP3, maybe due 1ldf sequence 68% similarity with AQP3 sequence, which quite ideal for homology modeling (16).

Figure 1: AQP3's modeling result from in front(left) and right side(right)

Figure 2: (a) binding site of asiatic acid, (b) Madecassic acid, (c) Asiaticoside, and (d) Madecassoside on AQP3

Table 1: binding energy and binding site of each ligand with AQP3

ligand	mean binding energy (kcal/mol)	binding site	
asiatic acid	-15.39	Ala 234, Ala 144	
madecassic acid	-16.77	Ala 234, Pro 140	
asiaticoside	-26.71	Ala 234, Ala 144	*
madecassoside	-24.98	Ala 234, Pro 140	*

* = with random bond created by glucose chain

As we can see at the results, all ligands that we compared here were attached on the same site (Alanine 234) with the highest binding energy. This result may suggested that Alanine 234 is the binding site of Asiatic acid, Madecassic acid, Asiaticoside, and Madecassoside. However, the binding energy of each ligand were different. Asiatic acid and Madecasic acid had lower mean binding energy at -15.39 kcal/mol and -16.77 kcal/mol respectively. While, Asiaticoside and Madecasoside had higher mean binding energy at -26,71 kcal/mol and -24.98 kcal/mol respectively. These higher mean binding energies may be caused by some bonds created by glucose-chain of Asiaticoside and Madecasoside.

With these numbers, we can suggest that Alanine 234 might be the binding pocket of Asiatic acid, Madecassic acid, Asiaticoside, and Madecassoside. However, further investigation required to ensure whether these binding energies can made stable complex AQP3. Asiaticoside and Madecassoside have a higher chance to form stable binding with AQP3 due their higher binding energies rather than Asiatic acid and Madecasic acid. These result also support Centella asiatica's phamacological value since the recent study from Hashim et al 2011, have confirmed that Asiaticoside and Madecasoside concentration in Centella asiatica were significantly higher than the concentration of Asiatic acid and Madecasic acid (7). The result of this study can be used as information for future in vitro studies on using target cell line.

Conclusion:

Asiatic acid, Madecassic acid, Asiaticoside, and Madecassoside are most likely have the same binding site at Alanine 234 of AQP3. Asiaticoside tent to have the highest binding energy and asiatic acid tent to be the lowest binding energy. Asiaticoside and Madecasoside maybe have higher binding energy because of their glucose chain can make some additional bonds to the protein. However, to ensure that binding energies were enough to made a stable complex with AQP3, further investigation required.

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