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Research Article

MOLECULAR DOCKING OF ALKALOID COMPOUND SA2014 FROM MARINE SPONGES *Cinachyrella anomala* TOWARDS P53 PROTEIN

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Abstract- p53 is a protein that induces apoptosis when DNA damage occurs. A mutated p53 protein involves in more than 50% of human cancers and possesses a role in breast cancer formation. Investigation for finding potential candidates anticancer drug that causes minimal side effects are generally obtained from nature, and sea sponges are currently explored. The purpose of this study was to determine a docking score and amino acids that play a role in an activity of alkaloid compounds from selected sponges *Cinachyrella anomala* SA2014 against protein p53. SA2014 compound has the ability as anticancer compounds against breast cancer T47D through the interaction of the amino acid leucine and phenylalanine. Leucine plays a role in the binding of p53 with SA2014 alkaloid compound that affected a resistance of cell cycle at G1 phase / S and triggered apoptosis. Furthermore, Phenylalanine stabilized p53 tetrameric structure through hydrogen bonds.

Keywords- *Cinachyrella anomala*, alkaloid SA2014, docking molecular, p53 protein.

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Introduction

A cycle cell is an important process in every organism because of its role in a cell division [1]. A cell cycle is controlled by a number of genes and if one of these genes changed its function it affects on the entire system of cell division. As a result, normal cells require a number of intrinsic mechanisms that involves molecular "gatekeeper" to avoid uncontrolled division. Formation and development of tumors is an example of uncontrolled division that occurs if a special protein that regulates cell division is changed its function, its gene expression or both. One of the proteins that are closely related to cell cycle control is p53 [2].

p53 is a transcription factor (protein regulator) that possesses a molecular weight of 53 kilodalton (kD) and was first discovered in 1979 [2, 3]. Normally, p53 controls cell cycle and induction of apoptosis [4]. If p53 loses its function it results in uncontrolled proliferation and causes cancer. P53 mutation is a genetic change that is discovered on more than 50% of human cancers [5]. Patients with p53 mutations have poor resistance in comparison to patients who did not have p53 mutations [6, 7]. Mutations in p53 are involved in a formation of breast cancer [8, 9, and 10].

According to the World Health Organization (WHO), cancer causes death every year with many increasing to 7.9 million people in 2007 and this number will increase to 80 million annually [11]. Furthermore, it is shown that breast cancer is classified as dangerous types of cancer. Treatments with cancer drugs generally serve to inhibit cell proliferation without turning off cancer cells and possess characters of multiple drug resistance (MDR) and resistant to cancer drugs [12]. Researcher to find potential candidates of new anticancer drugs is needed to answer these problems. Marine sponges are potential to be explored as anticancer drugs from nature that possesses less side effects and a specific bioactive compound [13].

Sponges is the largest contributor of bioactive compounds from the ocean (37%) and, followed by Coelenterate (21%), microorganisms (18%), algae (9%), echinoderms and tunicates respectively (6%), mollusks (2%) and bryozoans (1%) [14]. *Cinachyrella anomala* is a sea sponge which belongs to the class Demospongiae, order Tetractinellida, and family Tetillidae [15]. In this research, we tested bioactive compounds of *C. anomala* sponge SA2014 compounds against p53 protein and amino acids that play a role in protein-ligand interactions. Computational methods, which helped to determine the structure based drug design with docking score [16], were employed to determine important further drug design.

Materials and Methods

Methods The research was conducted from February to June, 2016, in the Laboratory of Zoology and animal engineering, Department of Biology, Faculty of Mathematics and Natural Sciences, Sepuluh Nopember Institute of Technology, Surabaya. Devices used in this research were a Netbook with processor Intel® atom™ with Windows 7 Operating System, 1 GB of RAM, PLANTS Protein Ligand ANT System software (http://www.tcd.uni konstanz.de/research/plants.php) by means of Co-Pendrivelinux KDE http://www. pendrivelinux. com), YASARA software (http://www.yasara.org), MarvinSketch ChemAxon software (http://www.chemaxon.com), and visual molecular dynamic software (VMD) [17]. The materials used in this research were discovered alkaloid SA2014 [25] drawed with Marvinskecth, Doxorubicin compound that is uploaded in the NCBI database and cyclin D1 (code 2W96 that is uploaded in the Protein Data Bank /PDB).

Preparation of protein target database was done by using YASARA in which data of the protein was saved in #.pdb format, and followed by deletion of unnecessary part from the system according to docking protocol. Hydrogen was added into the

system with the aid of YASARA, since resolution of the crystal structure could not be able to predict existence of the hydrogen. The result of preparation step was saved in protein. mol2 format. Modeling of the anticancer compound molecules from natural ingredients was conducted by drawing structure of the sample. Then, data of the sample structure from natural ingredients were drawn using MarvinSketch. Protonation of the compound was then checked at pH = 7.4, and the prepared data was saved in. mol2 format.

Simulation of the docking program was conducted by running pendrive linux, until the process was finished. Then, the best docking scored was conformed. The lowest score was chosen from the conformation. The lowest score was chosen from the conformation of the docking result. Then, YASARA was run; and the ligand and docking result were copied into YASARA. The docking result along with reference of the experiment was calculated using RMSD (Root Mean Square Deviation)

Results and Discussion

Targeted protein structure

Protein p53 binding to Murine Double Minute 2 (MDM2) has been used as a therapeutic target in breast cancer. Three-dimensional structure of the protein p53 obtained from PDB code: 1YCR by X-ray crystallography at 2.6 Å resolutions.

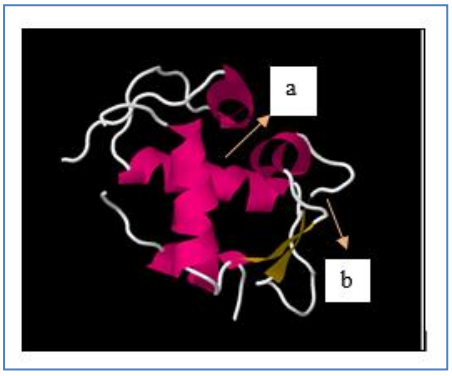

Fig-1 Three-Dimensional Structure Binds MDM2 protein with the p53 trans-activation domain (http://www.rcsb.org/pdb). Notes: a. MDM2; b. p53 trans-activation domain

p53 is a tumor suppressor protein as a master regulator of the signaling pathways vary. The role of p53 as a tumor suppressor protein, including the ability to hold the cell cycle, DNA repair, and apoptosis. The activity of p53 as a tumor suppressor protein would be disrupted if mutations occurred in both the p53 and MDM2. Oncoprotein MDM2 is a negative regulator that regulates the activity of p53 by inhibiting the p53 transcriptional activity directly. p53 protein activity can be stabilized by inhibiting the interaction between p53 and MDM2 [20].

A. Ligan's docking and Protein Target

Molecular docking performed to predict the likelihood of activity that occurs between the ligand to the target protein. One of the molecular mechanisms of anticancer is by inhibiting the activation of p53 proteins that bind to MDM2 play a role in cancer cell proliferation. Based on research, the results of docking between the target ligand and the protein p53 obtained 10 results conformation best value. The results showed that the alkaloid docking SA2014 has a score of -52.0728 docking in conformation to 6 is more stable compared with doxorubicin score of -50.6343 in conformations to 8. Inhibition of p53 molecules bind to MDM2 by alkaloid compounds SA2014 will generate biological responses such as proliferation inhibitory effect (anti-proliferation) which can be predicted through the scores obtained from the docking. Score is a strength parameter test ligand binding affinity for the receptor. The more stable ligand-protein interactions are reflected with the smaller score (minus) [17]. Values Distances) in YASARA software. Visualization of interactions between the molecular docking results was done using YASARA. Visualization of interaction to get the amino acids around the ligand was docked by using visual molecular dynamic (VMD).

Table-1 *Docking Ligand and p53Protein scorings*

Conformation	SA2014	Doxorubicin
entry_00001_conf_01	-51.8614	-49.9983
entry_00002_conf_01	-51.8600	-49.1915
entry_00003_conf_01	-51.7016	-49.5867
entry_00004_conf_01	-51.6456	-47.5193
entry_00005_conf_01	-50.7724	-49.1704
entry_00006_conf_01	-52.0728	-49.9439
entry_00007_conf_01	-52.0493	-50.4389
entry_00008_conf_01	-52.0076	-50.6343
entry_00009_conf_01	-51.2384	-49.9637
entry_000010_conf_01	-51.2131	-50.1500

docking score are listed in [Tables-1 and 2].

Table-2 *Docking ligand and p53protein selection*

Ligan	Skor *docking* terhadap p53
SA2014	-52.0728
Doxorubicin	-50.6343

Remarks: Ligand SA2014 = compound structure 1, 4, 9-triazatricyclo [7, 3, 1, 0] trideca-3, 5(13), 10-trien-8-ol marine sponges C. anomala, doxorubicin= anticancer drug.

B. Results on docking Ligan and Protein Target validation

Results of mean squared deviation - or root mean Root Mean Square Deviation (RMSD) atomic weight of the compounds docking with the reference was 1.0300 Angstroms. A protocol is acceptable if RMSD results compared with reference atomic weight of less than 2.0 Angstroms [17]. Therefore, protocol was acceptable for screening in an effort to work on the discovery of anticancer p53 protein T47D breast cancer.

C. Docking results visualization

Herewith are docking results between protein p53 to alkaloid compound SA2014 and protein p53 to doxorubicin using YASARA software.

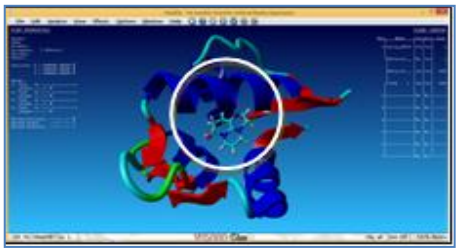

Fig-2 Visualisation of Docking SA2014 and p53 Protein using YASARA

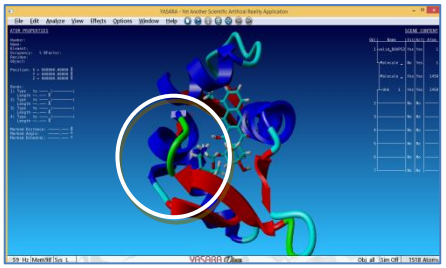

Fig-3 Visualization of Docking from Doxorubicin and p53 Protein using YASARA

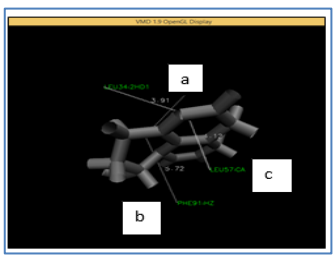

Fig-4 Visualization of Amino acids' distance around Ligand using VMD. a. Leucine 34; b. Phenylalanine 91 and c. Leucine 57

Amino acid that is near to the interaction between alkaloid compound SA2014 and p53 protein can be detected through bond distance of protein and ligand using Visual Molecular Dynamics (VMD) software. In addition, amino acids that is near to the interaction between alkaloid compound SA2014 and p53 protein is leucine 34 with a distance of 3.91 oA, 57 at 4:12 oA leucine and phenylalanine 91, which has a range of 5.72 oA.

Based on the results visualization using VMD, amino acids that close to ligand and protein interaction were phenylalanine and leucine. Phenylalanine is a receptor that plays a role in the p53-MDM2 bond with SA2014. The reason is phenylalanine is an amino acid found in the area tetramerisation area of p53 tumor suppressor protein. The amino acid phenylalanine is in the region of p53 interaction interface and it is important to stabilize the structure tetrameric through hydrogen bonds [21]. Therefore, if there is a mutation at amino acid, phenylalanine can change its tetrameric structure stability.

Leucine amino acid that played a role in binding of p53 and SA2014 would affect the resistance of the cell cycle at the G1 phase / S and trigger apoptosis. This is consistent with the theory that leucine stimulates mitochondrial biogenesis through the cell cycle [22, 23]. Furthermore, mitochondrial biogenesis and transcription mitochondria had been shown to occur early in the cell cycle, during the G1 phase. An abundance of leucine may play a role in the addition of caspase 3-mediated apoptosis [24]. Thus the activity of p53 with SA2014 through the role of the amino acid leucine is likely to trigger apoptosis in T47D breast cancer treatment

Conclusion

The alkaloid compounds SA2014 had a docking score of -52.0728 whereas doxorubicin scored of -50.6343. Furthermore, amino acids close to interaction between alkaloid compound of SA2014 and p53 protein is leucine and phenylalanine. SA2014 compound has ability as anticancer compounds against breast cancer T47D through the interaction of amino acid leucine and phenylalanine.

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Conflict of interest: None Declared

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