doi: 10.11594/jtls.01.02.03
THE JOURNAL OF TROPICAL LIFE SCIENCE
OPEN ACCESS Freely available online
VOL. 1, NO. 2, pp. 40 – 44, June 2018
Submitted April 2018; Revised May 2018; Accepted June 2018

Molecular Docking Study of Lycopene on Reducing the DNA-methyltransfer in Prostate Cancer

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ABSTRACT

Lycopene is a member of carotenoid family, and is naturally abundant in tomatoes. The consumption of lycopene is already needed for human because it acts as an antioxidant, meanwhile, our body cannot produce that naturally. Previous studies have shown that there is an inverse relationship between dietary lycopene intake and the risk of PCa. However, the study mechanism underlying how the lycopene affect or inhibit the control of cancer growth, in this case is DNA-methyltransferase (DNMT) that can regulates the cancer genes, is still limited, and even absent. Motivated by that, a series of method including preparation docking, molecular docking, and identifying the biological activity were done to study the mechanism of lycopene in reducing the DNMT. The result of lycopene-DNMT binding was compared with other known ligand that already known to bind the DNMT in its active site, which are SFG and SAH. The docking results showed that the binding affinity of lycopene and DNMT is lower than other ligand. The biological activity analysis also showed that lycopene is proven to have antioxidant activity, however, it still needs further study or experimental work to prove its ability for apoptosis agonist or as anti-proliferative disease because it is only computationally proven.

Keywords:*DNMT, lycopene, molecular docking, prostate cancer*

INTRODUCTION

Cancer is currently the second leading cause of death in the United States behind cardiovascular diseases. It is estimated that more than 1.6 million new cases of cancer were diagnosed in 2012 [1]. Because of the impact of cancer on the society, efforts to prevent or to treat cancer are an ongoing research interest [2]; including the exploration of its epigenetics mechanism. DNA methylation, catalyzed by the DNMTs, plays an important role in maintaining genome stability. DNA methyltransferases (DNMTs), responsible for the transfer of a methyl group from the universal methyl donor, S- adenosyl-L-methionine (SAM), to the 5-position of cytosine residues in DNA, are essential for mammalian development. DNMTs play an important role in genomic integrity, disruption of which may result in chromosome instability and tumor progression [3]. The methylated Several clinical trials using antioxidants and natural compounds have been conducted to observe if these compounds have anticancer or chemopreventive properties [2]. Lycopene is a potential antioxidant or nutrient protector. A number of epidemiological studies have shown an inverse relationship between dietary lycopene intake and the risk of PCa (Prostate Carcinoadenoma) [2]. Therefore, it is requires to do a research that shows the real relation between the cancer and lycopene. The purpose of this research is to do a molecular docking study to reveal the potential key binding interactions between Lycopene and DNMT enzymes [4]. Lastly, to prove that the site where lycopene binds to the active site of the target protein, other ligands that have proven to be bounded in the active site of DNA-methyltransferase, therefore, the result of the DNMT and lycopene can be compared with other ligand, especially in terms of the binding location [5].

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How to cite:
Sukirman AM (2018) Molecular Docking Study of Lycopmene on Reducing the DNA-methyltransferase in Prostate Cancer. J. Bioinfo. Biomedic. Research. Journal 1 (2): 40 – 44.

MATERIALS AND METHODS

Proteins

The crystal structures of human DNMT1 (PDB ID: 3SWR) and DNMT3A & DNMT3B (PDB ID: 2QRV) were retrieved from the Protein Data Bank (PDB), with SDF format file. The PDB archive contains information about experimentally-determined structures of proteins, nucleic acids, and complex assemblies. The DNMT3A and DNMT3B were separated individually from the protein structure of ID:2QRV.

Ligands

Compounds S-Adenosyl-L-Homocysteine (SAH), Sinefungin or Adenosyl-Ornithine (SFG), as well as the ligand of interest LYC (Lycopene) were also retrieved from Protein Data Bank. The download format is SDF/PDB file. The source of getting the ligand can be also using PubChem. The links from PubChem's chemical structure records to other Entrez databases provide information on biological properties.

Preparation Docking

The proteins/macromolecules downloaded from Protein Data Bank or other sources usually still containing other components that are not necessary for docking procedure, such as the other ligands that still bounded to the active sites of the proteins, such as water, zinc, etc, which can act as the inhibitor, as well as the overlapping amino acid from the structure. In consequences, the file might not be readable by the docking software. In order to avoid that, a method called preparation docking is needed to remove those components and therefore get a "clean" and ready-to-be-analyzed structure. The method is by opening the protein on a software, following by scanning all the sequences and checking if there is an unnecessary ligand, and finally removing those components. In this case, PyMOL were used for the preparation docking. PyMOL (https://www.pymol.org/) is a free and flexible molecular graphics and modelling package which can be also used to generate animated sequences. Other software can also be used, such as VegaZZ which is also a complete molecular modeling suite.

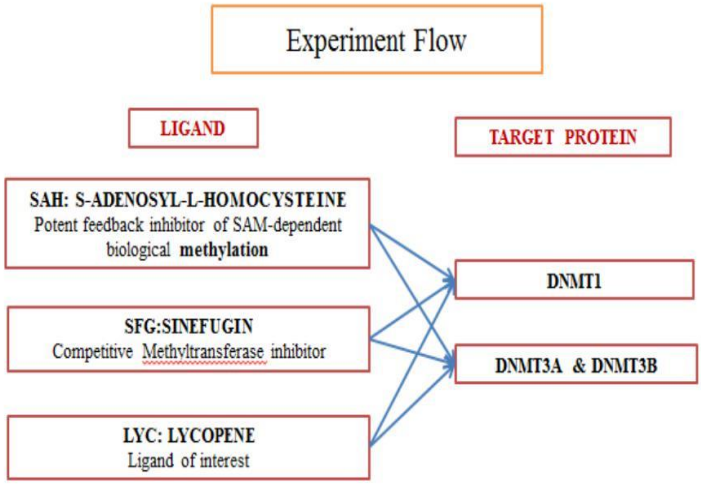


Figure 1. The experimental flow of docking target protein and ligand of interest

Docking

Molecular docking studies were performed using PyRx software GUI, and specifically used AutoDock Vina (vina.scripps.edu) software and Open Babel (file converting tool). PyRx is a virtual screening tool that allows the user to use a number of software, such as AutoDock Vina, Open Babel, and Python Shell. AutoDock Vina is an open-source program for doing molecular docking that was designed and implemented by Dr. Oleg Trott in the Molecular Graphics Lab at The Scripps Research Institute. The selected molecules or the target molecule is opened in AutoDock Vina in PyRx using Add Macromolecule feature, as well as opening the ligand by Add Ligand. The next process after the ligand and the target protein are chosen is to run Vina forward to get the docking result. The size of grid (the scope or the specific area to be analyzed) is need to be determined beforehand. The more precise

the size grid size, the better the result, since the area of binding can be analyzed more accurately. In this case, the grid is set to maximize because it is not known for sure where the lycopene, as well as the other ligand will bind to certain area in the target protein. The best binding models for each molecule were selected for the analysis.

Biological Activity Analysis

To make sure about the biological function of lycopene, a biological activity analysis is done using Pass Server. Pass server is used generally to get more information about biological potential of compounds. The biological activity of the compound of interest can be predicted on the basis of MOL-file, SMILES, or drawing in Marvin JS. SMILES file for lycopene is retrieved from PubChem. The output of analysis will be a list of different biological activities, following by the score of analysis that lies between 0 to 1. There are also two different threshold from the score; the score >0.3 means that it is proven by computational analysis and need to be further validation using experimental study; the score which is >0.7 means that that particular biological function of a compound is proven using both experimental and computational analysis. There are three biological activities which this study is focusing; the Apoptosis antagonist, Anti-proliferative disease, and Antioxidant.

Visualization

The result of experiment, such as the 3D structure, need to be re-visualized in order for people to understand better about the structure. The methods including labeling the molecule, re-color, etc. The software can be using PyMOL, YASARA, etc. However, this process is an optional (no visualization in the report).

RESULTS AND DISCUSSION

The evaluation of this study is about knowing whether the lycopene compound is by binding to the DNA-methyltransferase enzyme. Therefore, the analysis of the molecular docking binding is based on their binding affinity. Binding Affinity is the capability of ligands to form coordination bonds with a receptor. The binding affinity of a ligand with a receptor depends upon the interaction force of attraction between the ligands and their receptor binding sites. Protein–ligand binding occurs only when the change in Gibbs free energy (ΔG), Free energy (G°) = $-RT\ln K_b$, of the system is negative when the system reaches an equilibrium state at constant pressure and temperature [4].

Table 1. Docking result based on the binding affinity of lycopene and isoforms of DNMT.

Ligand	*Protein Target (DNMT)*	*Binding Affinity*
SAH: S-ADENOSY L-L-HOMOCYSTEINE	DNMT1	-8.5 kcal/mol
	DNMT3a	-7.9 kcal/mol
	DNMT3b	-9.4 kcal/mol
SINEFUNGIN	DNMT1	-8.9 kcal/mol
	DNMT3a	-6.6 kcal/mol
	DNMT3b	-9.3 kcal/mol
LYCOPENE	DNMT1	-7.6 kcal/mol
	DNMT3a	-6.5 kcal/mol
	DNMT3b	-6.5 kcal/mol

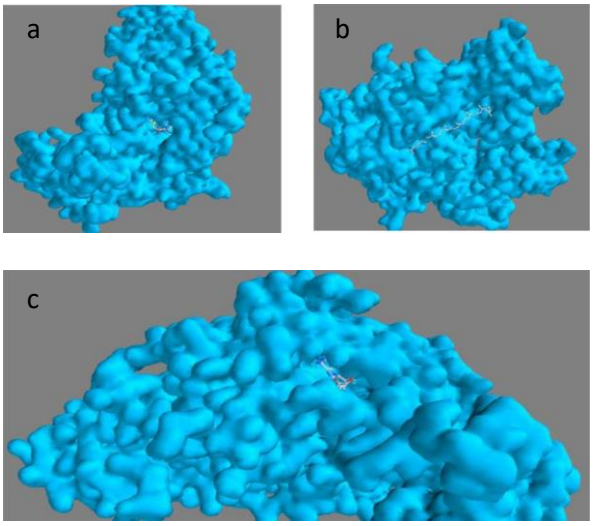
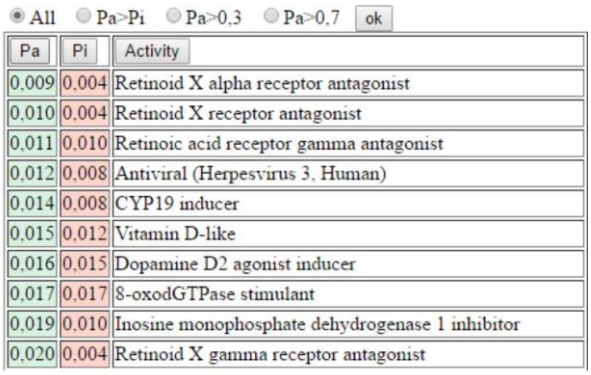


Figure 2. The docking visualization of DNA-methytransferase (DNMT) and a). S-Adenosyl-L-Homocysteine (SAH); b). Sinefungin (SFG); c). Lycopene

Based on the fact that the better the binding, the lower the binding affinity, from the docking result, lycopene meanwhile has the highest binding affinity compared to the SAH and SFG. Thus, it cannot be said that lycopene has a potential to inhibit DNMT by binding to its active site. Moreover, the binding location of each ligand is different, which is supporting the binding affinity result (Figure. 2). On the other hand, the biological activity of lycopene is analyzed using Pass Server (Figure 3).



All Pa>Pi Pa>0.3 Pa>0.7 ok

Pa	Pi	Activity
0.009	0.004	Retinoid X alpha receptor antagonist
0.010	0.004	Retinoid X receptor antagonist
0.011	0.010	Retinoic acid receptor gamma antagonist
0.012	0.008	Antiviral (Herpesvirus 3, Human)
0.014	0.008	CYP19 inducer
0.015	0.012	Vitamin D-like
0.016	0.015	Dopamine D2 agonist inducer
0.017	0.017	8-oxodGTPase stimulant
0.019	0.010	Inosine monophosphate dehydrogenase 1 inhibitor
0.020	0.004	Retinoid X gamma receptor antagonist

Figure 3. Analysis of lycopene activity using Pass Server

Table 2. Biological activity analysis result of lycopene

No.	*Biological Property*	*Score (Pi)*
1.	Apoptosis agonist	0.392 Pa (Pi=0.008)
2.	Anti-proliferative disease (Proliferative disease treatment)	0.478 Pa (Pi=0.021)
3.	Antioxidant	0.848 Pa (Pi=0.003)

The table above shows the biological activity property of lycopene from Pass Server result (Figure 3), following by its potential score. The first analysis is apoptosis agonist. The word "agonist", according to online biological dictionary is a molecule that combines with a receptor on a cell to trigger physiological reaction, and full agonist means that is has an affinity for and activate a receptor [5]. Therefore, this test is to check whether lycopene has any property to induce the apoptosis event in cancer cells. The score of apoptosis agonist is 0.392, which means that it is proven only by computational experiment, but need to be confirmed by experimental study. Cancer is categorized as proliferative disease. According to NCBI, proliferative disease is a unifying concept that excessive proliferation of cells and turnover of cellular matrix contribute significantly to the pathogenesis of several diseases, including cancer, atherosclerosis, rheumatoid arthritis, psoriasis, idiopathic pulmonary fibrosis, scleroderma and cirrhosis of the liver, is presented [6]. The score of 0.478 in anti-proliferative property also reveals that lycopene is proven to have such ability in general. However, it is not yet proven by experimental study to state that lycopene has the ability for proliferative disease treatment. The last analysis is antioxidant. Generally, this analysis is just to validate that the software doing its job by correctly predicted that lycopene is proven computationally and experimentally to have antioxidant property, as many studies have stated before.

CONCLUSION

Previous studies showed that the consumption of lycopene affect the prostate-antigen serum, which means that it might have some relations with curing prostate cancer. This experiment triggered this study to reveal the potential of lycopene to become an alternative or the new drug for prostate cancer treatment, especially using molecular docking that showed the binding affinity of lycopene to DNA-methyltransferase (DNMT) which acts as one of the main mechanism in cancer growth. However, the result showed that lycopene has higher binding affinity compared to the other ligand that is proven to bonded to the active site of DNMT in normal condition. A series of biological activity analysis revealed that there still the need of proving the lycopene to involve in other mechanism in cancer development or treatment for future studies.

ACKNOWLEDGMENT

Author thanks to Indonesia International Institute for Life Sciences for facilitating that make this research available and get result that can published to public.

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