Potential analysis *Persea americana, Allium sativum* and *Ficus sepatica* as anti-cancer uses in silico docking and ADMET prediction

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Abstract. Cancer has been a major cause of death in several countries, according to a recent report from the International Agency for Research on Cancer (IARC) which more than 300,000 cases diagnosed and killed reaching 145,000 people. Indonesia has provided lots of resources that has capability as anti-cancer. This study aimed to discover bioactivity of potential compound from several Indonesian’s plants i.e *Persea americana, Allium sativum* and *Ficus sepatica* to prevent cancer based on reverse docking studies by using PyMOL v1.7.4.5 Software (Schrödinger), the PyRx 0.8 software and SwissAdme Prediction. The seed of Avocado *Persea americana* has terpenoid that has a potential in cancer inhibitor with Aldo-Keto Reductase family 1 member B10. The main compound of garlic *A. sativum* is S-allylcysteine and Lysine-specific demethylase as target protein. *Ficus sepatica* has Antofin as potential compound and Steroid 17-alpha-hydroxylase as the protein. The binding affinity value are -7.8, -5.1 and 8.9 respectively.

1. Introduction

Cancer is still considered the leading cause of death for some people. This is because, most cancers are diagnosed after they spread throughout the body and are already in the final stages. Cancer is a cell disease characterized by the loss of the control function of cell cycle regulation and cell homeostatic function in multicellular organisms. With this failure, cells cannot proliferate normally and will proliferate continuously, causing abnormal tissue [1].

Rapid technological developments, make researchers in the world to continue to look for ways to treat cancer. Many studies have been conducted to find something that can function as an anticancer. Research by utilizing compounds contained in plants that have the potential as anti-cancer [2]. As a tropical country rich in biological resources, Indonesia has ± 30,000 plant species and ± 7000 species discovered as medicinal plants, such as anti-inflammatory, anticancer or antimicrobial [3,4]. The plants that is widely known and used extensively by the people of Indonesia are *Persea americana, Allium sativum* and *Ficus sepatica*.

The active compounds of herbs is one alternative development in research for new anticancer because it is believed to have minimal side effects. Lot of researches has done in the field of natural products for cancer drug discovery. Currently, it has found in *Persea americana, Allium sativum* and *Ficus sepatica* and a single active compound isolated from herbal plants that has potential as an anticancer. From the results of literature review found that Triterpenoid, S-Allyl-L Cystein, and Antofin known to be able to overcome cancer [6,5,7] Thus, the author chooses plants *Persea americana, Allium sativum* and *Ficus sepatica* to prove that the presence of compounds that contained in these plants can potentially overcome and treat cancer that will be tested by In silico by using docking, which is one new discoveries in the field of Bioinformatics.
2. Materials and Methods

2.1. Ligand Preparation

The chemical structure in Triterpenoid (*Persea americana*), S-Allyl-L Cystein (*Allium sativum*), and Antofin (*Ficus sepatica*) was obtained from several supporting literature, 3D structure and Conical SMILES. The Triterpenoid ligand, Conical SMILES C=CCSCC(C(=O)O)N S-allylcysteine ligand, and Conical SMILES CC(=O)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)OC(=O)C)C)C Antofin ligand were obtained from the Pubchem database (https://pubchem.ncbi.nlm.nih.gov/) with CID number: 451674, 9793905, and 11013784 respectively. The 3D structures of the these ligand are changed in the PDB format using Avogadro.

2.2. Target Selection

Identification of target proteins for docking is used by 2 bank data, namely SuperPred (http://prediction.charite.de) and Swiss Prediction Target (www.swisstargetprediction.ch), proteins are validated using Uniprot (https://www.uniprot.org). The protein used in this study are Aldo-Keto Reductase family 1 member B10 (*Persea americana*), Lysine-specific demethylase (*Allium sativum*), and Steroid 17-alpha-hydroxylase (*Ficus sepatica*). Furthermore, the protein that were collected and validated than proteins were prepared using clean protein to remove the water molecules from the structure, PyMol software is used.

2.3. Molecular Docking, Molecular Visualisation and Target Protein

Molecular docking was carried out using PyRx 0.8 by reacting protein Aldo-Keto Reductase family 1 member B10 (*Persea americana*), Lysine-specific demethylase (*Allium sativum*), and Steroid 17-alpha-hydroxylase (*Ficus sepatica*). Furthermore, the protein that were collected and validated than proteins were prepared using clean protein to remove the water molecules from the structure, PyMol software is used.

2.4. Compound Prediction with ADMET

Swissadme is used to predict the prediction and significant descriptors of Druglikeness properties of the compounds that can be tolerated using (www.swissadme.ch). Druglikeness is a term to explain how physicochemical properties of a compound affect molecular properties in vivo through various requirements such as the lipinski rule, Ghose, Veber, Egan dan Muegge rule.

3. Results and Discussion

The main compound contained in Avocado seeds (*Persea americana*) namely Triterpenoid, Triterpenoid a class of compounds widely reported to have anticancer activity. Group compounds triterpenoids have cytotoxic activity against cell lung cancer A549, colon HCT15, leukemia HL-60, liver HepG2, breast MCF-7, HeLa, gastric SGC-7901, and the skin SK-MEL-2 [8]. The working mechanism of triterpenoids is by disrupting the mitochondrial membrane permeability in the cells or cause cells to undergo necrosis and death [9]. The ethanol extract positive avocado seed containing groups of secondary metabolites such as alkaloids, flavonoids, phenols, saponins, tannins, and triterpenoids [10].

Aldo-keto reductase family 1 member B 10 (AKR1B10), also known as aldose reductase-like-1 (ARL-1), had been found from PHC (Primary hepatocellular carcinoma). Growing evidence has confirmed that AKR1B10 is associated with the development and progression of many cancers such as hepatocellular carcinoma, smoking-related non-small-cell lung cancer, esophageal adenocarcinoma, gastric cancer, breast cancer, cervical cancer, and pancreatic cancer. The research has already found that inhibiting of AKR1B10 can reduce the risk of cancer around 50% [11].

The structure of the compound *Persea americana* (Triterpenoid) and the target protein was visualized in 3D using PyMOL applications (Figure 1) and to determine the potential of compounds as anti-cancer. Triterpenoid with Aldo-Keto target protein reductase family 1 member B10 using the
docking technique. Based on the docking results show the value of binding affinity as the bond between triterpenoid compounds and target proteins is -7.8.

**Figure 1.** Binding Site of Triterpenoid (Blue) with Aldo-Keto Reductase family 1 member B10 (green) Triterpenoid

For the second plant, the main compound found in garlic (*Allium sativum*) is *S*-allylcysteine, this compound interacts with one of the Lysine-specific demethylase 4C. Lysine-specific demethylase 4C or KDM4C role is likely paradox because it has a function which capable with pc2 as a an activator of growth control cell and KDM4C regulation also was proven that it can reduce breast cancer . However if this protein is overexpression, it will contribute to tumor formation [12].

The structure of *Allium sativum* (*S*-allylcysteine) and target proteins is visualized in 3-dimensional form using the Pymol application as in (Figure 2.) and to determine the potential of *S*-allylcysteine compounds as anti-cancer especially in the mouth interacted with KDM4C target proteins using techniques docking. Based on the docking results show the value of binding affinity as a binder between the compound *S*-allylcysteine and the target protein.

Hydrogen (H) -bonds are ubiquitous in nature and play an important role in protein-ligand interactions, and catalysis [13], protein-ligand binding only occurs when changes in free energy from the negative system when the system reaches a state of balance at constant pressure and temperature [14]. The value of lower binding affinity has the potential to bind with protein because the energy needed to interact between compounds and target proteins is lower. KDM4C interact with natural compounds found in *Allium sativum* (*S*-allylcysteine) which has been visualized in 3D using Pymol. The Binding Affinity value between *S*-allylcysteine and KDM4C target protein is -5.1

**Figure 2.** Binding Site of *S*-allylcysteine (Orange) with Lysine-specific demethylase 4C or KDM4C (green)
For the third plants, Antofin in *Ficus sepatica* was known can inhibit the signaling pathways between the receptor with a chemical compound derived from cancer cells. The resulting inhibition of signals from the cancer cells can not be captured by the receptor so that no further processing. This causes the cancer cells can not meet the needs of nutrients and oxygen, and therefore cannot survive [15,16].

Ligands search showed that only one type of ligand that is owned by the two sites that CYP17A1. This protein is also known as a human gene of the protein Steroid 17-alpha-hydroxylase / 17,20 lyase. The target gene function is the Conversion pregnenolone and progesterone into the product 17-alpha-hydroxylated and subsequently into dehydroepiandrosterone (DHEA) and androstenedione. Catalyzes the 17-alpha-hydroxylation and 17,20-lyase reaction. Involved in sexual development during fetal life and at puberty [16].

**Figure 3.** Binding Site of *Antofin* (Red) with Steroid 17-alpha-hydroxylase (green)

Based on molecular docking, the protein Steroid 17-alpha-hydroxylase with Antofin has binding affinity by -8.9. The drugs used in cancer consists of corticosteroid, sex hormones, and procarbazine asparaginase. Often used with good results, on the types of cancers that depend on hormones, whose growth can be inhibited by androgen or estrogen, or anti-hormones, such as estrogen given to prostate cancer (in order to negate the effects of male hormones). Androgens are given to breast cancer. CYP17A1 genes regulate human sex steroid biosynthesis through lyase activity of 17a-hydroxylase / 17,20 and is the target of an anti-cancer drug Abiraterone prostate.

**Table 1.** Binding affinity of fruit compound

| Ligan and Receptor                                    | Binding Affinity |
|-------------------------------------------------------|-----------------|
| Triterpenoid and Aldo-Keto Reductase family 1 member B10 | -7.8            |
| *S*-allylcysteine and Lysine-specific demethylase 4C or KDM4C | -5.1            |
| *Antofin* and Steroid 17-alpha-hydroxylase              | -8.9            |

Table 1 Show the result of Binding affinity from molecular docking of *Persea americana*, *Allium sativum* and *Ficus sepatica* compound. Binding affinity value is the value that shows the ability of a compound to bind to a receptor. Low binding affinity value indicate the affinity between receptor and ligand is higher, and vice versa [17], from all of the compound, Antofin in *Ficus sepatica* has the lowest binding affinity value. It means that antofin has the highest potency to become drug compound as anti cancer.
Ligands of *Persea americana*, *Allium sativum* and *Ficus sepatica* compounds have chemical and physical properties that can be used as drug the possibility can damage the mitochondrial membrane permeability in the cells or cause cells to undergo necrosis and death in human cancer cells during meet Lipinski rule. Result shows that Triterpenoid meet Lipinski, Ghose, Veber, Egan and Muegge rule with a score of 0.55.

4. Conclusion

This study proved that Triterpenoid, *S-allylcysteine*, and *Antofin* contained on *Persea americana* (Seed Avocado), *Allium sativum* (Garlic) and *Ficus sepatica* have potential as a anti-cancer based on its binding affinity with -7.8, -5.1 and -8.9 respectively and intermolecular interactions. Based on ADMET prediction, Triterpenoid, *S-allylcysteine*, and *Antofin* are also potential as an anti-cancer drug according to *Lipinski, Ghose, Veber, Egan dan Muegge* rule.

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