Effect of Active Compound of Pasak Bumi Root (Euricoma longifolia, Jack) as an inhibitor of CDK2 methylation: In Silico Study

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Effect of Active Compound of Pasak Bumi Root (*Euricoma longifolia*, Jack) as an inhibitor of CDK2 methylation*: In Silico* Study

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Abstract. Active compound of Pasak Bumi's root, a native plant of Indonesia, is used as antitumor by triggering cell apoptosis and reactivating the silence tumor suppressor gene caused by hypermethylation, inhibiting cancer cell proliferation. The aim of this study is to know the role of quassinoid from Pasak Bumi's root (*Eurycoma longifolia* Jack) as an inhibitor of CDK2 methylation *in silico*. This is a descriptive study. CDK2 samples are obtained from Protein Data Bank (RSCB.org) with ID3SWR, samples of natural quassinoid are obtained from PUBCHEM NCBI and controlled by Sunitinib (®Sutent). Autodock Vina program PyRx 0.8 is used to analyze Molecular Docking. The process of analyzing molecular interactions is carried out using the LigandScout V.2.0 program. Visualization process are carried out using LigandScout V.2.0 program. The affinity of quassinoid and sutinab to CDK are -6.1 and -9.4, respectively. The more negative the binding affinity value, the better the ability of the compound (ligand) to bind to the receptor (macromolecules). From this case, Sutinab has better value compared to quassinoid. Target protein analysis using HITPICK shows quassinoid's target predictor is JUN protein. Protein interaction analysis are obtained, and the compound is using stitch. JUN protein and Sunitib could bind with CDK2. The conclusion of this study is Sutinib has greater affinity compared to quassinoid.

Keywords : herbal compound, quassinoid, Pasak bumi root, antiproliferation, CDK2, prostate cancer cell line

1. Introduction

In United States 2014, around 233,000 new cases and around 29,480 deaths from prostate cancer [1]. The etiology of prostate cancer is still controversial. Genetic and epigenetic play a role in the process of prostate cancer carcinogenesis. Genes that experience mutations in prostate cancer are the p53, p16 (CDKN2A), PTEN, bcl-2, race, p27 (CDKN1B), and caspase genes [2,3]. The p27 tumor suppressor gene (p27 gene) is a gene that has hypermethylation in prostate cancer. The p27 gene is proven to be activated by hypermethylation promoter in prostate cancer [2], whereas PTEN inhibits AKT phosphorylation, which is required for activation and targets many effectors [4]. PTEN may loss (events that are common in the treatment of poorly differentiated and resistant prostate cancer) and cause activation of the P13K / AKT pathway and subsequent apoptotic resistance [5]. Restoration of PTEN activity in prostate cancer cells PTEN deficiency has been shown to increase sensitivity and encouraging apoptosis [6].

Based on above, prostate cancer epigenetic changes occur due to hypermethylation of tumor suppressor genes p27 and PTEN. The reversible nature of epigenetic changes in cancer results in the possibility of epigenetic therapy as an alternative treatment. The aim of epigenetic therapy is to reverse the causes of epigenetic changes that occur in cancer so that the normal epigenome condition returns. DNA methylation inhibitor compounds are the first epigenetic drugs proposed as drugs for cancer therapy.

Herbal therapy can be an alternative. Several types of bioactive components derived from herbs that have the ability to inhibit the work of the DNA methyltransferase (DNMT) enzyme can affect DNA methylation processes and have barriers to cancer activation through reactivation of tumor suppressor genes that experience silencing [6-14]. Flavonoids can reactivate suppressor tumor genes that have undergone silencing due to hypermethylation [15,16].

Eurycoma longifolia Jack or the Pasak Bumi plant can be an alternative herbal therapy choice. Pasak bumi is a tropical plant belonging to the Simaroubuceae family that is distributed in Southeast Asian countries, native plants in South Kalimantan [17]. *Eurycoma longifolia* has biological active ingredients found in the roots. Pasak Bumi (*Eurycoma longifolia* Jack) is one of the plants that has been used as a drug for detoxification, free radical antioxidants, and anticancer [18,19]. The compounds contained in E. longifolia are quassinoid [18,20,21] and 9-methoxycantin-6-on alkaloids [22,23] and canthinone alkaloids [24]. Quassinoid is a triterfenoid compound that has a flavonoid-like structure so that the Pasak Earth root quassinoid compound has the potential as a demethylating agent.

Cheah and Azihmahtol's [25] study showed that methanol extract of E. longifolia can induce apoptosis in MCF-7 breast cancer cell line through a decrease in Bcl-2 expression [25]. 9-methoxycantine-6-on compounds from methanol extract and chloroform E. longifolia have a cytostatic effect on ovarian cancer cells (CaOv3), epidermoid carcinoma (KB), breast cancer (MCF-7) and rhabdosarcoma (RB) [22]. Conscience research in vitro and in vivo using ethanol extract on breast cancer cells produced inhibitory activity of COX-2 expression, decreased BCl-2 expression, increased Caspase 3, increased expression of p53, increased expression of p21, increased expression of GADD45 and decreased Ras [26]. This shows that the *E. longifolia* Jack has the potential as a new active drug for cancer suppression.

Based on the thinking above the active compound of the Pasak Bumi root (*E. Longifolia* Jack) has cytotoxic effects on various cancers such as colon cancer, breast cancer, lung cancer, skin cancer (melanoma), ovarian cancer, and others, it is necessary to know whether it is also cytotoxic in prostate cancer that is independent androgen (hormonal resistant therapy). According to author's knowledge, study on the potential of the Pasak Bumi's roots is still few especially study for hypermethylation, and inhibiting cancer cell proliferation in Prostate Cancer (PC-3 CDK2). This later became the background of the authors to conduct research on the potential of Pasak Bumi's roots in inhibiting proliferation and increasing apoptosis in PC-3 Prostate Adenocarcinoma cells. The aim of this study is to know the role of quassinoid from Pasak Bumi's root (*Eurycoma longifolia* Jack) as an inhibitor of CDK2 methylation in Prostate Cancer (PC-3) *in silico*.

2. Materials and Methods

2.1. Design

This study using descriptive method to identify the Quassinoid compound found in the roots of Pasak Bumi (*E. longifolia* Jack) and identify its potential in antiproliferation *in silico study*,. For positive control ligand, this study used Oral, small-molecule Sunitinib (marketed as Sutent by Pfizer), is a multi-targeted receptor tyrosine kinase (RTK) inhibitor that is approved for treatment of renal cell carcinoma (RCC) and imatinib-resistant stromal gastrointestinal tumor (GIST) on January 26, 2006. Sunitinib was approved as the first line for cancer drug in two different indications.

2.2. Procedure

2.2.1. The Interaction between Pasak Bumi's Quassinoid and PTEN(CDK2). CDK2 samples are obtained from Protein Data Bank (RSCB.org) with ID3SWR. This model is human CDK2 protein which has been linked to an inhibitor, while a sample of quassinoid natural ingredients is obtained from PUBCHEM NCBI and controlled by Sunitinib (®Sutent). The potential of each compound in inhibiting CDK2 was analyzed by looking at the affinity of the compound in binding to the active side of CDK2. The Molecular Docking analysis process is done using Autodock Vina on the PyRx 0.8 program. The Docking process is carried out on the active side of the CDK2.

8 Result and Discussion

The aim of this study is to know the role of quassinoid from Pasak Bumi's root (*Eurycoma longifolia* Jack) as an inhibitor of CDK2 methylation in silico. This study found that the quassinoid has an affinity as inhibitor of CDK2. In this study, the composition of silico study are ie Quassinoid Analog as ligand, CDK2 (3TI1) as macromolecule, and **SUNITINIB** *(*C_{22} H_{27} F N_4 O_2) as Positive control ligand. The affinity of quassinoid and Sunitinib to CDK are -6.1 and -9.4, respectively (Table 1). Ligand's ability to bind with receptor (macromolecule) is shown by its negativity towards binding affinity, the more negative the binding affinity value, the better the ability of the compound (ligand) to bind to the receptor (macromolecules). In this case, Sunitinib has better value compared to quassinoid means Sunitinib has better ability to bind than quassinoid

Table 1. Result.

	Quassinoid (Binding affinity)	Sunitinib (Binding affinity)
CDK2	-6.1	-9.4

To analyse target protein of quassinoid after binding, HITPICK was used. As seen in figure 1, Protein target analysis using HITPICK shows that the target prediction of the quassinoid is JUN protein. Then the interaction analysis between protein and compounds is done using stitch. JUN proteins and Sunitinib could bind with CDK2. CDK2 Serine / threonine-protein kinase is involved in cell cycle control, meiosis, and triggers duplication of centrosomes and DNA. CDK2 has an important role in regulating a good balance between cellular proliferation, cell death, and DNA repairing in human embryonic stem cells (hESCs). By binding the quassinoid to CDK, the cellular profileration and cell death may be balanced. Figure 2 explained this mechanism, If P21 / P27 is not phosphorylated, the CDK2 activity increases, increasing tumorigenesis and abnormal cell cycle regulation. P27 is a CDK inhibitor. Drugs that work in inhibiting CDK2 have a function to arrest the cell cycle.

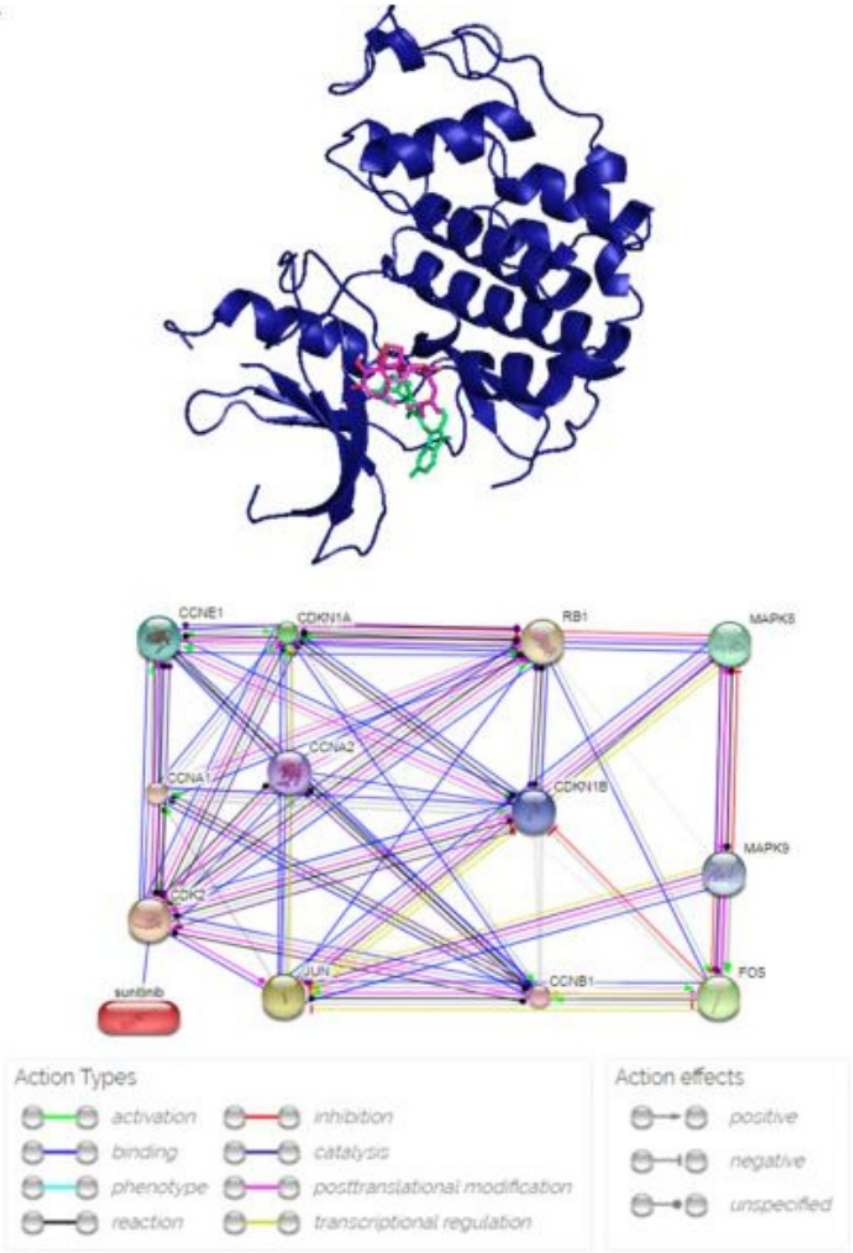

Figure 1. Action type and effect toward CDK2. Green line: Sunitinib. Pink line: Quassinoid.

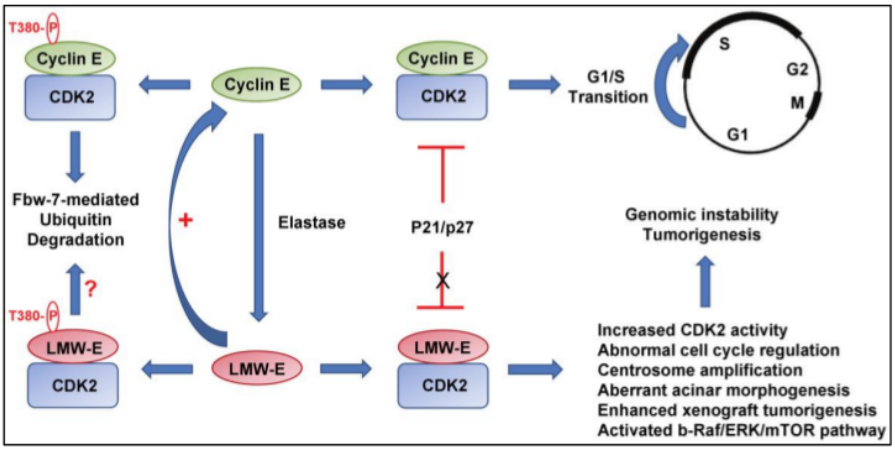

Figure 2. CDK2 Regulation in tumorigeneses.

The limitation of this study is there is no other marker or protein whom assessed. Future study with more protein involvement is needed.

4. Conclusion

The role of quassinoid of Pasak Bumi's root (*Eurycoma longifolia* Jack) is an inhibitor of CDK2 methylation as in silico study with a lesser affinity compared to Sunitinib.

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