Research Article

Evaluating the potency of active compounds from *Eurycoma longifolia* jack roots extract as prostate cancer therapy

Eka Yudha Rahman¹,², Didik Huswo Utomo³, Mulyohadi Ali⁴, Basuki Bambang Purnomo⁵, Nia Kania⁶

**ABSTRACT**

**Aim and Scope:** Prostate cancer will occur when immortal cells develop in the prostate gland. It was frequently diagnosed in men and becomes the fourth most common cancer in the world in 2014. In Indonesia, it has high prevalence of about 16 cases in 100,000 of men. Furthermore, Indonesia has an endemic plant called *Pasak Bumi* (*Eurycoma longifolia* Jack) which is well-known as traditional medicine and cancer therapy. The root extract of *Pasak Bumi* consists of eurycomanone, quassinoid, and canthin. Therefore, this study aimed to predict the potency of *E. longifolia* active compounds as prostate cancer therapy.

**Material and Methods:** There are four essential protein targets in prostate cancer such as *Bcl-2*, *RAS*, *MAPK*, and *CASP*. The three-dimensional structure of active compounds was retrieved from PubChem, and protein target was downloaded from Protein Data Bank. The interactions were calculated using Pyrx.0.8. Thus, the molecular interaction was analyzed using LigPlus. Moreover, the biological activity of the active compound was analyzed using PASS server. **Results and Discussion:** Results showed that each active compound is strongly bind to RAS and only RAS -quassinoid complex which has the lowest binding affinity score about −9.3 Kcal/mol. Based on the structure-activity relationship analysis, only eurycomanone and quassinoid which potentially involved in the anticancer mechanism as antineoplastic and apoptosis agonist. It means these compounds are blocking the active site of RAS protein to inhibit the cell proliferation. **Conclusion:** It can be concluded that all active compounds have the lowest binding affinity to RAS. Moreover, quassinoid is the most active compounds which have the influence to RAS. It shows that quassinoid potentially as a therapeutic agent.

**KEY WORDS:** Anticancer, Apoptosis, Canthin, Eurycomanone, Herbal compound, Inhibitor, Prostate cancer, Quassinoid

**INTRODUCTION**

Prevalence of prostate cancer in Indonesia is around 16 cases per 100,000 of men.¹ Moreover, prostate cancer is including to the top 10 most common cancer in men. It according to data collected from 13 national histopathology centers throughout Indonesia.² There are several therapy for prostate cancer patients such as hormone therapy and radiation therapy,³⁴ but they have a lot of side effect and high cost. Therefore, the specific molecular mechanism of prostate cancer becomes a particular concern in research to find the solution.

Genes that involved in the prostate cancer were located on the chromosome number 1 such as *p53*, *Bcl-2*, *RAS*, *p21*, and caspase.⁵ The family of *Bcl-2* plays an important role in the apoptosis, such as *Bcl-2* and *Bcl-xL* were decreasing the apoptosis, while *Bax*, *Bik*, and *Bid* were increasing the mechanism of apoptosis.⁶ There are two pathways of apoptosis such as intrinsic and extrinsic.⁶ The intrinsic pathway induced by cellular stress involving *Bcl-2* and *caspase-9* while extrinsic pathway induced by reaction of ligand binding which involving *Fas* and *caspase-8*.⁷ Therefore, *Bcl-2*, *RAS*, *caspase-9*, and *MAPK* could be the essential protein target in prostate cancer.

Indonesia is well-known as mega biodiversity and has a lot of herbal medicine species. *Pasak Bumi* or *Eurycoma longifolia* jack is one of the herbal medicine species that have been well-known as traditional medicine in Indonesia.
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longifolia Jack is one kind of endemic plant in South Borneo, Indonesia. It belongs to Simaroubaceae family[8] and believes have a function as an aphrodisiac. Furthermore, roots of Pasak Bumi are known consist of an essential active compound such as eurycomanone, quassinoid, and canthin as anticancer.[9] Based on the recent research, quassinoid known had cytotoxic effect in the colon cancer, breast cancer, lung cancer, and fibrosarcoma[10]. Therefore, this study aimed to predict the potency of *E. longifolia* active compounds as prostate cancer therapy based on in silico approach.

**MATERIALS AND METHODS**

**Retrieval Data**

Three three-dimensional (3D) structure of an active compound from Pasak Bumi roots extract such as eurycomanone (CID 13936691), quassinoid (CID 5458870), and canthin (CID 97176) was collected from PubChem (www.pubchem.ncbi.nlm.nih.gov). Moreover, the 3D structure of protein target in prostate cancer, Bcl-2 (PDBID 4XLQ), caspase 9 (PDBID 1NW9) RAS (PDBID 2CE2), and MAPK (PDBID 4QTA) were downloaded from protein data bank (www.rcsb.org/pdb/home/home.do). The 3D structure was provided for molecular docking [Figure 1].

**Molecular Docking**

The docking process was carried out using AutoDock Vina in Pyrx 0.8 to compute the binding affinity between ligands (active compounds of Pasak Bumi) and protein target. Each of active compound was docked to the specific active site of protein target.[11]

**Molecular Interaction**

The molecular interaction between active compound and protein target was analyzed by LIGPLUS Program.[12] The result determination was based on the amino acid interaction. The active compound would be determine as potential inhibitor if they had interacted to amino acid in the active site of protein target.

**Molecular Visualization**

All biomolecules were visualized using CHIMERA 1.8.1 to generate the representative figure.[13]

**Analysis of Biological Activity**

The active compounds of *Pasak Bumi* were analyzed using PASS online server to determine the biological activity. It depended on the compound structure. The analysis will be resulting probability of active (Pa), and the probability of inactive (Pi) score with a range from 0 to 1. If Pa > Pi mean, it is potential for a specific therapeutic candidate.[14]

**RESULTS AND DISCUSSION**

Three active compounds of Pasak Bumi were able binding to the active site of protein target. Moreover, eurycomanone, quassinoid, and canthin have a strong to RAS which indicated by lower binding affinity score than another complex. It indicated by the most minimum binding affinity score which is about −9.3 Kcal/mol [Table 1].

In the normal conditions, activation of RAS triggers a cellular response and transformation. Furthermore, it also to be an essential component of signaling network for controlling cell proliferation and survival through the RAS-MAPK pathway.[15] Moreover, it is known involving in the prostate cancer development, progression, and metastasis.[16] It proven by recent research which states that RAS protein was found in 43% of primary prostate cancer samples and 90% of metastatic samples.[17] It is indicate that RAS protein is potentially as therapeutic agent for prostate cancer.

![Figure 1: The 3D structure of (a) Active compound of *Pasak Bumi* roots and (b) Protein target of prostate cancer](image-url)
Based on the UniProt database, gross domestic product was bind to the active site of RAS protein. It could be used as a promising template to screen the potential inhibitor for prostate cancer inhibition. The active site of RAS protein is around on the Gly15, Lys16, Asn116, Ala146, Ser145, Asp119, Leu120, Asp30, Lys117, Ala18, Cys32, Gly13, Ser17, and Phe25 residues.

Figure 2 shows that each active compound was bind to inhibition site of RAS protein and interact to several amino acids around of that site. However, only quassinoid which has the appropriate bond to inhibition site of RAS protein on the residues Gly15, Lys16, Asp30, Phe28, Lys117, Glu31, Pro34, Gly12, Ser17, and Asp33 through 2 hydrogen bonding and 9 hydrophobic bonding.

Furthermore, the determination of biological activity shows that eurycomanone and quassinoid have Pa > Pi for antineoplastic and apoptosis agonist with the values ranges from 0.8 to 1 [Figure 3]. However, canthin shows antineoplastic activity with lower value ranges from 0.2 to 0.4, then it has not apoptosis agonist activity. The value of Pa and Pi can be considered to be measures of the compound to study belonging to active and inactive compounds, respectively. However, among the three active compounds of Pasak Bumi, eurycomanone, and quassinoid are the most potential for therapeutic agent. These compounds may suppress the prostate cancer development by blocking the active site of RAS protein for decreasing the proliferation rate.

CONCLUSION

Active compounds of E. longifolia Jack root extract (quassinoid, canthin, and eurycomanone) predicted to have an effect to inhibit the cell proliferation in prostate cancer which is involving as an inhibitor of Bcl-2, RAS, and MAPK. Furthermore, they are triggering the activation of caspase-9 for increasing the process of apoptosis. All of the active compounds have the lowest binding affinity to RAS. Moreover, quassinoid is the most active compounds which have influence to RAS. It shows that quassinoid potentially as a therapeutic agent.

ACKNOWLEDGMENT

This work supported by the Laboratory of Bioinformatics, Department of Biology, Brawijaya University.

REFERENCES


Source of support: Nil; Conflict of interest: None Declared