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In Silico Analysis of Picfeltarraenin IA and IB as Potential PI3K and EGFR Inhibitor

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ABSTRACT

Picfeltarraenin IA and IB are the steroid glycoside from Picria fel-terrae Lour., Have been traditionally used in medication. Epidermal growth factor receptor (EGFR) plays a critical role in the initiation and progression of a variety of human cancers, including breast cancer. An important signaling pathway downstream of EGFR is the PI3K/AKt pathway, which regulates cellular processes as diverse as cell growth, survival, proliferation and migration. In silico docking using PLANTS program and visualized by Yasara program. The model of three dimension enzyme structures used in this research were EGFR and Phosphatidylinositol-3-kinase (PI3K), binding pocket with the Protein Data Bank (PDB) code 1M17 and 3DBS . Two and three dimension of Picfeltarraenin IA, IB and ZSTK474 as the standard were generated using Marvin Sketch program. Both compounds and ZSTK474 inhibited EGFR and PI3K with docking score -101.7930; -104.6410, -91.7920 and -90.6176 -87.7705; -94.7491 respectively.

Keywords: Picfeltarraenin IA and IB, EGFR, PI3K, inhibitor, in silico.

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer and the second leading cause of cancer death among females [1]. Moreover, breast cancer ranks as the fifth cause of death from cancer overall (522,000 deaths), is the most frequent cause of cancer death in women in less developed countries (324,000 deaths, 14.3% of total), and the second cause of cancer death in developed countries (198,000 deaths, 15.4%) after lung cancer. A recent study reported that breast cancer is leading in the estimated new cancer cases, and the second most common death cause among women suffering from cancer in the USA [2].

Epidermal growth factor receptor (EGFR) is a member of the HER family of transmembrane receptors that regulate cellular processes as diverse as cell survival, cell proliferation, and apoptosis. Aberrant expression of this receptor on the cell surface or its enhanced activity may contribute to cancer incidence [3,4]. Deregulated EGFR signaling causes cancer cells to be refractory to anticancer therapies, including immunotherapy, chemotherapy or radiotherapy [5].

The phosphatidylinositol-3-kinase pathway regulates cell growth and proliferation and is often dysregulated in cancer due to mutation, amplification, deletion, methylation, and post-translational modifications. This pathway is in intracellular signaling pathway important for apoptosis, malignant transformation, tumor progression, metastasis and radioresistance [6,7]. Phosphatase and tensin homolog (PTEN) is a negative regulator of the PI3K/Akt/mTOR pathway [8]. PTEN is highly effective tumor suppressor and frequently mutated, deleted, or epigenetically silenced

in various human cancers including breast cancer [9,10]. Due to the important role of the PI3K pathway in cancer research, many valuable inhibitors targetting one signal node (single inhibitor) or two nodes at the same time (dual inhibitor) in the pathway have been developed in recent years. In the last decade, significant progresses have been made in developing combination therapy with PI3K inhibitor with other therapy to overcome less effective therapy. The role of EGFR and PI3K in cancer progression was showed in Figure 1.

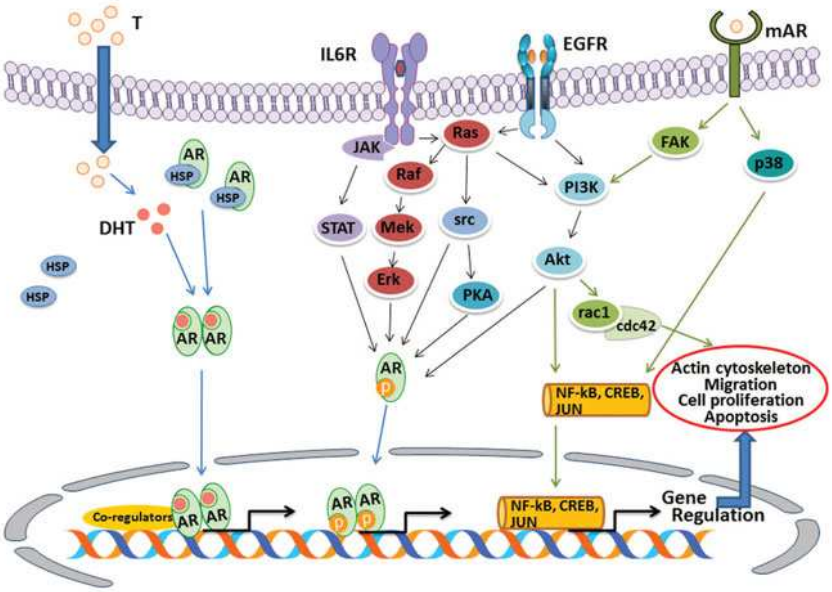


Figure 1. EGFR and PI3K pathways in cancer development

Picria fel-terrae Lour. (Linderniaceae) in Indonesia commonly known as poguntano, the herb used in traditional medicine in Asia especially in Indonesia to treat fever, abscess, herpes infection, traumatic injury, and snake bite [11]. Modern pharmacological investigations indicated that the extract of Picria fel-terrae Lour. exerts diuretic, antypiretic, hepatoprotective, cardioprotective, antidiabetic, antioxidant, anti-inflammatory, anthelmintic, and analgesic activities [12-17]. Moreover, *Picria fel-terrae* inhibits hepatitis B (HB) e-antigen excreted by HepG2 2215 cell lines, suggesting to have anti-HB virus activity [18]. It can be developed as co-chemotherapeutic regimen for breast cancer by inducing apoptosis and cell cycle arrest and suppressing cyclin D1 and Bcl-2 expression [19,20]. These biological activities have been attributed to the chemical compound present in *Picria fel-terrae*, such as triterpenoid saponin, phenylethanoid glycosides, and flavonoid glucorinides [21,22]. Triterpenoid saponins especially Picfeltarraenin IA and IB are the main bioactive for the complement-inhibiting properties which can partly explain its traditional use in treating inflamation or degenerative diseases [23]. The chemical structures of Picfeltarraenin IA, IB and ZSTK474 are showed in Figure 2 and 3.

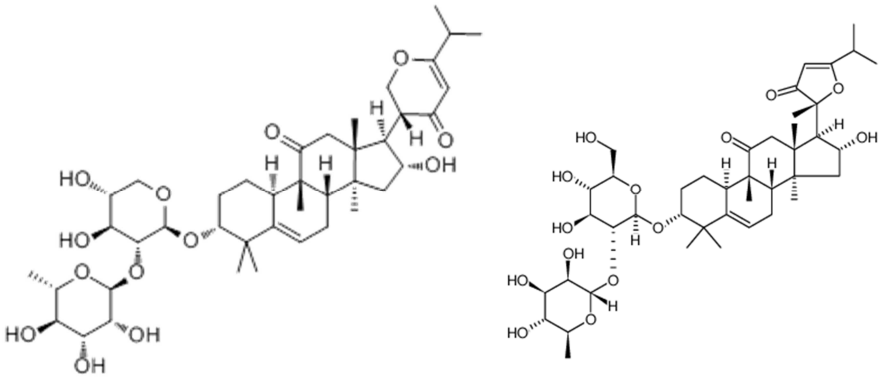


Figure 2. Structure of Picfeltarraenin IA and IB

Computational methods are being developed to predict the activity of compounds. In silico approaches contribute significantly to beginning pharmaceutical research and important in target discovery. The need of timely adaptation and application of in silico approaches in pharmaceutical research has clearly been recognized and is expected to improve further to get an efficiency in drug discovery [24]. The purpose of our study was to identify how PI3K

inhibitors are working for cancer using in silico molecular docking method. The purposes of this research was to assess the activity of Picfeltarraenin IA and IB in inhibiton EGFR and PI3K with in silico method.

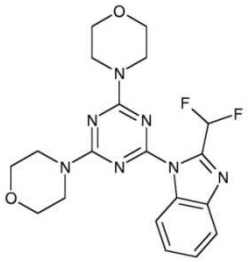


Figure 3. Structure of ZSTK474 as selective inhibitor of PI3K

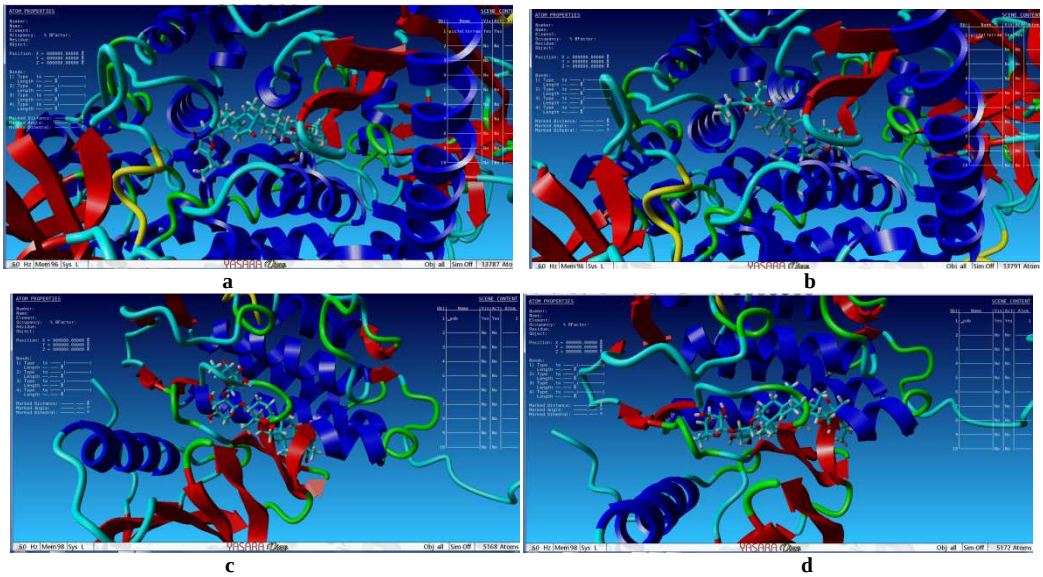
MATERIALS AND METHODS

Aspire E1-470 series operated by Windows 7 Home Premium, Intel® Core™ i3 -3217U (1,8 GHz, 3MB L3 cache), 32-bit, hard disc drive 500 GB and RAM memory 2 GB DDR3 L were used to run the molecular docking process. In silico docking using PLANTS program and visualized by Yasara program. Co Pen Drive Linux KDE program was used to connecting Windows operation system to Linux operation system. The model of three dimension of enzyme structure used in this research was PI3K binding pocket with the Protein Data Bank (PDB) code 3DBS and 1M17 for EGFR. They were obtained through from http://www.rscb.org/pdb. Two and three dimension conformation models of Picfeltarraenin IA, IB and ZSTK474 as the standard PI3K inhibitor were generated by Marvin Sketch program.

RESULTS

Table 1. Docking score between ligand and protein target

No	Ligand Name	Docking Score	
		PI3K	EGFR
1	ZSTK474	-94.7491	-91.7920
2	Picfelterraenin IA	-90.6176	-101.7930
3	Picfelterraenin IB	-87.7705	-104.6410



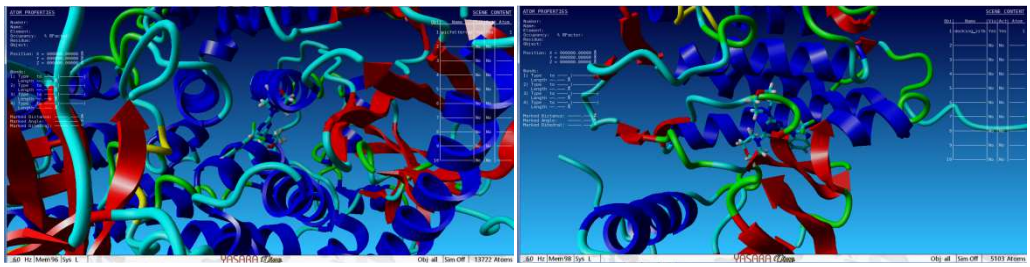
a **b**

c **d**

Figure 4. Visualization of interaction between
(a) picfeltarraenin IA with PI3K, (b) picfeltarraenin IB with PI3K
(b) picfeltarraenin IA with EGFR, (d) picfeltarraenin IB with EGFR

GD9 which was crystallized in the structure of 3DBS PI3K and AQ4 for EGFR binding pocket were extracted and docked again into its original PI3K binding pocket. The Root Mean Square Deviation (RMSD) values resulted from these ligand docking were 1,5761 Å for 3DBS and 1,6970 Å for 1M17. The RMSD was obtained less than 2.0000 Å indicating that the docking methods were valid [25]. In silico docking between picfeltarraenin IA and IB into the

3DBS and 1M17 binding pocket result in the docking score in Table 1 is showed the results of docking score into 3DBS and 1M17 binding pocket. Figure 4 and 5 are showed the results of visualization of picfeltarraenin IA, IB and ZSTK474 to EGFR and PI3K using Yasara.



a **b**

Figure 5. Visualization of interaction between
(a) ZSTK474 with PI3K, (b) ZSTK474 with PI3K

DISCUSSION

The docking score represents the binding affininty of the ligand to the target protein. The docking of PI3K and EGFR target with compounds using docking procedure revealed that all the computationally predicted lowest energy complexes of PI3K and EGFR are stabilized by intermolecular hydrogen bonds and stacking interactions [26]. Docking score of Picfelterraenin IA and IB were lower than ZSTK474 as kinase inhibitor especially PI3K but higher in inhibition of EGFR. In silico drug design can play a significant role in all of stages of drug development from preclicial assesment to the end of clinical development [27]. The results were obtained at in silico screening have shown that it represents the best step (way) to get an accurate result in a short time and saving manner [28].

PI3K pathway plays important roles in tumor initiation and progression, including those in proliferative activity and in apoptosis. PI3K signaling is also commonly associated with the metastatic cascade in carcinoma. Although several aspects of tumor inhibition are not fully understood, numerous small molecule inhibitors targeting the PI3K pathway is currently being studied in clinical trials [29]. There are strong relationship between EGFR and PI3K, PI3K/AKT/mTOR signaling is frequently deregulated due to mutations affecting one of its upstream regulators the EGFR receptor and other components within the pathway [30].

CONCLUSION

Picfelterraenin IA and IB are steroid glycoside from *Picria fel-terrae* Lour. They were showed to have the activity in inhibition of cancer growth through EGFR and PI3K pathways and they are potential to develop as anticancer.

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Conflict of interest
There is no conflict of interest to be reported

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