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Bioinformatics: Cheap and Robust Method to Explore Biomaterial from Indonesia Biodiversity

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Abstract. Indonesia has a huge amount of biodiversity, which may contain many biomaterials for pharmaceutical application. These resources potency should be explored to discover new drugs for human wealth. However, the bioactive screening using conventional methods is very expensive and time-consuming. Therefore, we developed a methodology for screening the potential of natural resources based on bioinformatics. The method is developed based on the fact that organisms in the same taxon will have similar genes, metabolism and secondary metabolites product. Then we employ bioinformatics to explore the potency of biomaterial from Indonesia biodiversity by comparing species with the well-known taxon containing the active compound through published paper or chemical database. Then we analyze drug-likeness, bioactivity and the target proteins of the active compound based on their molecular structure. The target protein was examined their interaction with other proteins in the cell to determine action mechanism of the active compounds in the cellular level, as well as to predict its side effects and toxicity. By using this method, we succeeded to screen anti-cancer, immunomodulators and anti-inflammation from Indonesia biodiversity. For example, we found anticancer from marine invertebrate by employing the method. The anti-cancer was explore based on the isolated compounds of marine invertebrate from published article and database, and then identified the protein target, followed by molecular pathway analysis. The data suggested that the active compound of the invertebrate able to kill cancer cell. Further, we collect and extract the active compound from the invertebrate, and then examined the activity on cancer cell (MCF7). The MTT result showed that the methanol extract of marine invertebrate was highly potent in killing MCF7 cells. Therefore, we concluded that bioinformatics is cheap and robust way to explore bioactive from Indonesia biodiversity for source of drug and another pharmaceutical material.

Keywords: bioinformatics, Virtual screening, Protein-protein interaction, pathway analysis, biomaterial

INTRODUCTION

Indonesia has a very high biodiversity that potential as a source of pharmaceutical and drugs materials. However, the biodiversity has not been explored yet to find new materials for the drug or another pharmaceutical agent. The main obstacle to exploring is due to the lack of supportive government policies and funds for conduct fundamental research in Indonesia(1,2). So it is necessary to develop methods that are cheap, fast and robust for exploring of potency of the biodiversity. Several studies have shown that the bioinformatics approach can be used to analyze the molecular target of the compound(3). The analysis was based on the similarity of molecular structure with drug that has been known its receptors. Furthermore, the target molecule can be analyzed its role in the cell.

The role of protein in a cell can be predicted based on its interaction with other proteins(4). Protein-protein interactions are assumed to develop cascade and drive molecular mechanisms within the cell(5). Therefore, by knowing the protein-protein interactions, we can figure out the role of protein in physiological and molecular

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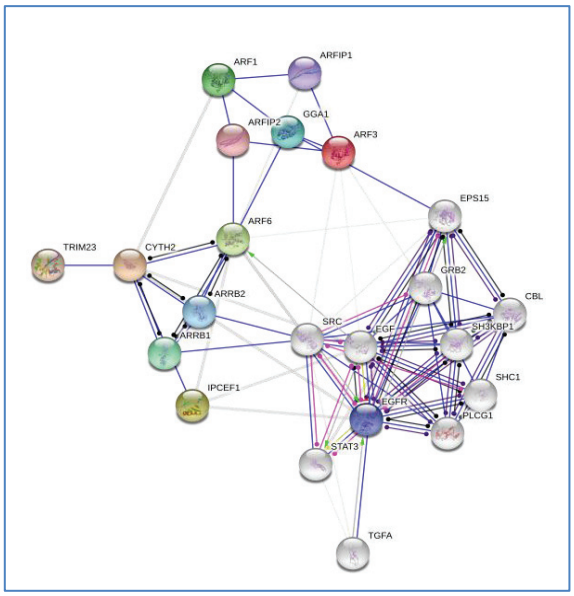
pathways in the cell(6–8). Therefore, activity and toxicity of small molecule or compound can be predicted based on their protein target. If we know the active compound or metabolite produced by organism, then we can predict the potency of the organism to obtain the new biomaterial. This study discusses the application of bioinformatics as robust and cheap method to explore biomaterials.

METHODS

The robust and cheap exploration to obtain potency of biodiversity can be done by using virtual screening. The method is built based upon the available information from published articles and molecular database such as NCBI, ZINC, and drug Bank. The First step is collect information of active compound that may contain in a plant or animal. Then, draw structure of the active compound by using PubChem sketcher V 2.4 (Http: // PubChem.ncbi.nlm.nih.gov/search/search.cgi#). After drawing the structure, then convert to the simplified molecular-input line-entry system (SMILES) formula to predict molecular target or protein target. SMILE is a line notation for describing the structure of chemical species using short ASCII strings. Target molecules were predicted based on the similarity to the most similar compound in the set of known interactions as well as on the rank of the target's score by HITPICK software(http://mips.helmholtz-muenchen.de/hitpick/cgi-bin/index.cgi?content=targetPrediction.html). Furthermore, the protein targets were analyzed its interaction with another protein to predict the protein network that possibly occur in the cell by using STRING Database (http://string-db.org/). Proteins involved in the interaction were then analyzed its role in regulating the cellular mechanisms and molecular pathways by using Panther DB (http://pantherdb.org/). Further analysis to validate the virtual screening result should be done in wet-lab, either *in vitro* or *in vivo*.

RESULTS AND DISCUSSION

Every organism, both flora and fauna, always produce metabolites that have meaning for pharmaceutical. Hereafter the metabolites could be examined their activity and protein target based on their structure. The target protein could be predicted by using HITPICK based on the SMILE structure of the metabolite. The SMILE could be degenerated by using PubChem sketcher V 2.4.



Term	p-value	n°
Cancer	1.000	4
Disease of cellular proliferation	1.000	4
Disease	1.000	5
Primary immunodeficiency disease	1.000	1
Disease of anatomical entity	1.000	1
Job's syndrome	1.000	1
Hyperimmunoglobulin syndrome	1.000	1
B cell deficiency	1.000	1
Immune system disease	1.000	1

Term	p-value	n°
ErbB signaling pathway	2.080e-10	8
Glioma	5.430e-7	6
Endocytosis	1.629e-5	9
Non-small cell lung cancer	1.769e-5	5
Focal adhesion	1.769e-5	5
Pathways in cancer	1.769e-5	7

FIGURE 1. The protein interactions were constructed from target genes of dictyostatin (Left), and these genes have a significant role in cancer disease (right).

Here we discuss the application of bioinformatics screening of anti-cancer from marine invertebrate that contain dictyostatine compounds. The molecule targets of dictyostatine were predicted by using HITPICK. The compound has two targets, namely CYTH2 and ARF3. Further, the proteins targets were analyzed proteins interaction followed by pathway analysis (Figure 1). Results indicated that the proteins target of dictyostatine has a role in cell proliferation and cancer diseases, also involved in erbB signaling and glioma pathways (Figure 2). Virtual screening results suggested that the invertebrate has anti-cancer activity.

Since the invertebrate has potency for anti-cancer, then we have validated the result in the wet lab. The methanol extract of the marine invertebrate was used to treat cancer cells (MCF7), *in vitro*, WST-1 protocol (Roche). The results showed that the methanol extract was able to kill cancer cells in a dose-dependent manner (Figure 3). Taken together, the bioinformatics method provided robust and cheap method to explore the potency of biodiversity.

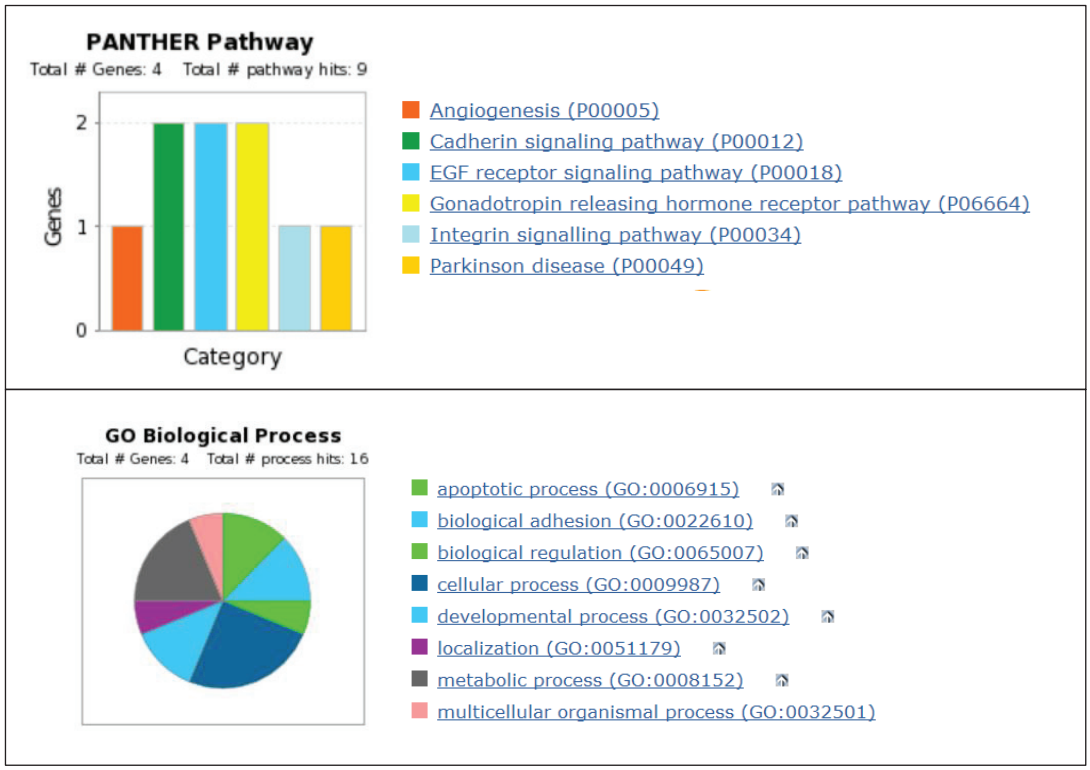


FIGURE 2. The role of genes involved in cancer disease, which is extracted from the proteins interaction. The Gens involved in angiogenesis and growth signaling pathway (above), as well as having a role in apoptosis (bottom).

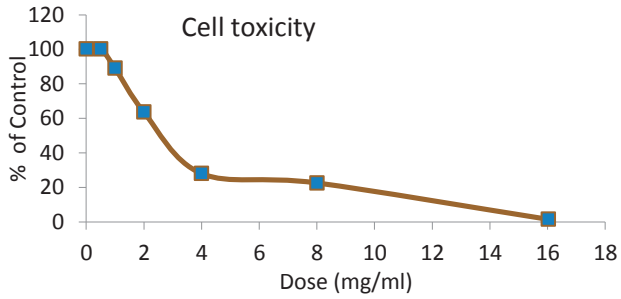


FIGURE 3. The methanol extract was able to kill the cancer cells in a dose-dependent manner.

CONCLUSION

Bioinformatics method has demonstrated its ability to be used to screen the pharmaceutical potency of organism, that warrant for robust and cheap for exploring biomaterial from Indonesia biodiversity.

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