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NATURAL BIOACTIVE COMPOUND FROM *MORINGA OLEIFERA*AGAINST CANCER BASED ON IN SILICO SCREENING

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Graphical abstract

Abstract

Cancer is the leading cause of death in the world. More than 10 million people worldwide are expected to be diagnosed with cancer, a disease commonly believed to be preventable. *Moringa oleifera* is one of the well known as a local plant as food and health plant in Indonesia. Anticancer is one of potential treatment found in *Moringa oleifera* seed, leaves, and pods extracts. This study aimed to discover natural bioactivity compound from *Moringa oleifera* for anticancer. Niazimicin is one of bioactive compound found in *Moringa oleifera* reported have potent antitumor promoting activity. The bioinformatics tool used in this study were: Pubchem compound database, protein target prediction database Pharmmapper and Chemmapper, molecular docking software PyRx 0,8, ligand docking and binding site analysis with PyMOL and LigPlus software. To check for compound's drug-likeness were applied using DruLiTo software. Based on our previous steps, we found that niazimicin interacted with glycosyltransferase via hydrogen bond and hydrophobic interactions. Niazimicin is the best Glycosiltransferase inhibitor based on binding afinity (-7,3 kcal/mol) that is more negative than existing glycosiltransferase inhibitor, such as tert-Butyl 4-(5-formyl-2-thienyl)piperazine-1-carboxylate, sialic acid and fucose. According to Lipinski's rule parameter we discover that Niazimicin is a potential anticancer drug.

Keywords: Glycosiltransferase, *Moringa oleifera*, niazimicin, reverse docking

1.0 INTRODUCTION

Cancer is the leading cause of death in the world. More than 10 million people worldwide are expected to be diagnosed with cancer. Cancer continues to be a worldwide killer, despite the enormous amount of research and rapid developments seen during the past decade (1). *Moringa oleifera* is one of the well knowas a food and health plant in Indonesia. Various parts of this plant such as the leaves, roots, seed, bark, fruit, flowers and immature pods used as many kind of medical treatment. Anticancer is one of potential treatment found in *Moringa oleifera* seed extracts (2). Anti tumor promoting activity of the leaves and pods of *Moringa oleifera* has also been reported. Niazimicin is one of bioactive compound found in *Moringa oleifera*reported have potent anti tumor promoting activity (3).

2.0 OBJECTIVE

This study aimed to discover natural bioactivity compound from *Moringa oleifera* for anticancer based on insilico sreening.

3.0 METHODOLOGY

3.1 Ligand Preparation

Chemical 3D structure and SMILES of ligand (Niazimicin) taken from pubchem compound database (https://pubchem.ncbi.nlm.nih.gov/) with number ID: CID 5471459.

3.2 Target Selection

Input Niazimicin's SMILES to Pharmmapper (http://lilab.ecust.edu.cn) to identify potential target candidates using pharmacophore mapping approach (4) and Chemmapper (http://lilab.ecust.edu.cn/chemmapper/) using pharmacology and chemical structure association based on molecular 3D similarity method (5).

3.3 Molecular Docking

Then molecular docking Niazimicin, target protein, and known inhibitors of target protein used PyRx 0,8 software.

3.4 Visualization of Molecule and Small Molecule Interaction

The interactions between niazimicin, target protein, and known inhibitors of target proteinvisualyzed and analyzed using PyMoland LigPlus.

3.4 Compound's Drug-likeness

To prioritize drug-like phytomolecules, DruLiTo software was used to screen molecules based on eight filters namely Lipinski's rule (6).

4.0 RESULTS AND DISCUSSION

As the result of target selection using pharmmapper (job ID: 150713191316) and chemmapper database (job ID: 34079), it was discovered that Niazimicin interacted with Histo-blood group ABO system transferase in human body. The ABO variants were associated with risk of pancreatic cancers hepatocellular cancer (7). Histo-blood group ABO system transferase express glycosyltransferases (GTs) that play essential roles in many biological processes (8). Fact, that significantly higher levels of glycosyltranferases were found in the breast cancer specimens compared to the background tissue (9). Glycan is one of glycosyltransferase activities product. Glycans play several roles in different step of tumor progression regulating tumor proliferation, invasion, metastasis, and angiogenesis (10). So that glycosyltranferases become an interesting object of study for drug development since inhibitors of glycosyltranferases can potentially interfere pathological processes. Selective and effective inhibition of glycosyltransferasesprovides a promising strategy for drug development for the treatment of cancer disease (11).

Reverse docking is proving to be a powerful tool for drug repositioning and drug rescue. It involves docking a small-molecule drug/ligand in the potential binding cavities of a set of clinically relevant macromolecular targets (12). Based on reverse docking of glycosyltransferase (PDB ID: 1LZ0) with 1.80 Å resolution, niazimicin and known inhibitor of glycosyltransferase there are sialic acid, fucose and 5-formylthien-2-yl group (13) it could be inform that niazimicin has a most negative binding afinity (-7,4 kcal/mol) than tert-Butyl 4-(5-formyl-2-thienyl)piperazine-1-carboxylate (-6,1 kcal/mol), sialic acid (-5,7 kcal/mol) and fucose (-4,9 kcal/mol).

As the result of Visualization of molecule and small molecule interaction using PyMOL software we found that tert-Butyl 4-(5-formyl-2-thienyl)piperazine-1-carboxylate bind protein target (Glycosyltransferase) interacted with Glycosyltransferase via hydrogen ond and hydrophobic interactions of Phe 121, Cys 209, Val 210, Phe 270, Thr 119, Phe 121, and Asp 211 (Figure 1).

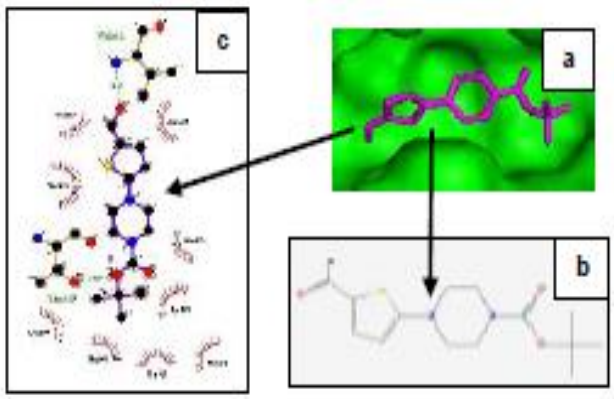

Figure 1 Result of molecular docking 3D structure between protein target (Glycosyltransferase) and tert-Butyl 4-(5-formyl-2-thienyl)piperazine-1-carboxylate. (a) tert-Butyl 4-(5-formyl-2-thienyl)piperazine-1-carboxylate (magenta) bind protein target (Glycosyltransferase) (green). (b) chemical structure of tert-Butyl 4-(5-formyl-2-thienyl)piperazine-1-carboxylate. (c) interaction between tert-Butyl 4-(5-formyl-2-thienyl)piperazine-1-carboxylate and protein target (Glycosyltransferase), LigPlot show that tert-Butyl 4-(5-formyl-2-thienyl)piperazine-1-carboxylate bind protein target (Glycosyltransferase) interacted with Glycosyltransferase via hydrogen bond and hydrophobic interactions of Phe 121, Cys 209, Val 210, Phe 270, Thr 119, Phe 121, and Asp 211

Niazimicin interacted with glycosyltransferase via hydrogen bond and hydrophobic interactions of Phe 121, Cys 209, Phe 270, Thr 119, Phe 121, Val 210, and Asp 211 (Figure 2).

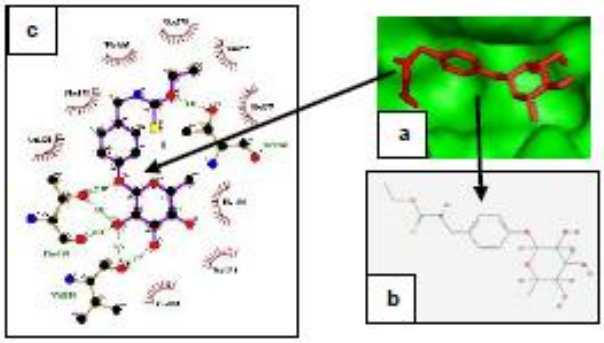

Figure 2 Result of molecular docking 3D structure between protein target (Glycosyltransferase) and Niazimicin. (a) Niazimicin (red) bind protein target (Glycosyltransferase) (green). (b) chemical structure of Niazimicin. (c) interaction between Niazimicin and protein target (Glycosyltransferase), LigPlot plot show that niazimicin interacted with Glycosyltransferase via hydrogen bond and hydrophobic interactions of Phe 121, Cys 209, Phe 270, Thr 119, Phe 121, Val 210, and Asp 211

Sialic acid interacted with Glycosyltransferase via hydrogen bond and hydrophobic interactions of Phe 121, Cys 209, Phe 270, Thr 119, Val 210, and Asp 211 (Figure 3).

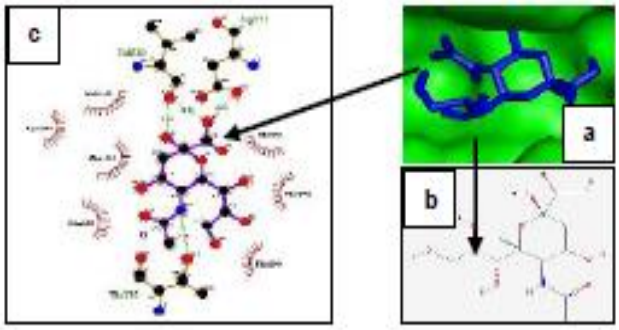

Figure 3 Result of molecular docking 3D structure between protein target (Glycosyltransferase) and Sialic acid. (a) Sialic acid (blue) bind protein target (Glycosyltransferase) (green). (b) chemical structure of Sialic acid. (c) interaction between Sialic acid and protein target (Glycosyltransferase), LiPlot plot show that Sialic acid interacted with Glycosyltransferase via hydrogen bond and hydrophobic interactions of Phe 121, Cys 209, Phe 270, Thr 119, Val 210, and Asp 211

Fucose interacted with glycosyltransferase via hydrogen bond and hydrophobic interactions of Phe 121, Cys 209, Phe 270, Thr 119, Val 210, and Asp 211 (Figure 4).

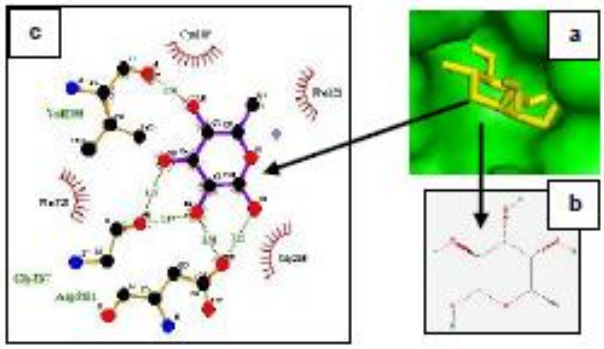

Figure 4 Result of molecular docking 3D structure between protein target (Glycosyltransferase) and Fucose. (a) Fucose (yellow) bind protein target (Glycosyltransferase) (green). (b) chemical structure of Fucose. (c) interaction between Fucose and protein target (Glycosyltransferase), DimPlot plot show that Fucose interacted with Glycosyltransferase via hydrogen bond and hydrophobic interactions of Phe 121, Cys 209, Phe 270, Thr 119, Val 210, and Asp 211

Using bioinformatic tools it was discoved that bioactive compund of *Moringa oleifera*, niazimicin bind glycosyltransferase at the same binding site with Glycosyltransferase's inhibitors, tert-Butyl 4-(5-formyl-2-thienyl)piperazine-1-carboxylate, sialic acid and fucose (Figure 5).

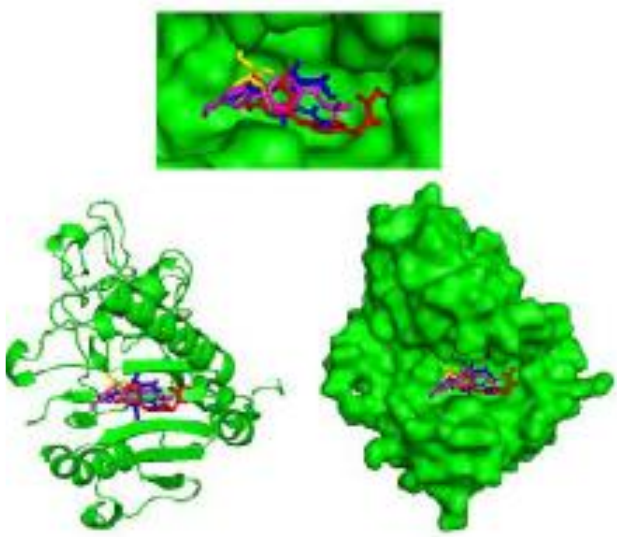

Figure 5 Interaction between protein target (Glycosyltransferase) and inhibitors (niazimicin, sialic acid, fucose) show that inhibitors bind the protein target at the same site. Information: green (Glycosyltransferase), red (niazimicin), blue (sialic acid), yellow (fucose), magenta (tert-Butyl 4-(5-formyl-2-thienyl)piperazine-1-carboxylate)

The study demonstrated that the 5-formylthien-2-yl group blocked a significant conformational change upon substrate binding and locked the enzyme in an unproductive conformation, and thus inhibit the GalTs activity (14). Sialic acid and fucose are unnatural sugar precursor could be used as potential

Glycosyltransferase inhibitors since it could be metabolically converted to the corresponding sugar nucleotide donor analog by the cell and then inhibit Glycosyltransferase as it bound but not used as a substrate by the enzyme (15). So it can be said that niazimicin has the same function like tert-Butyl 4-(5-formyl-2-thienyl)piperazine-1-carboxylate, sialic acid and fucose, sialic acid and fucose as inhibitors of Glycosyltransferase. Using DruLito software, we found that niazimicin is a potential anticancer drug according to Lipinski's rule parameter (Table 1).

Table 1 Drulito result using Lipinski's rule parameter to check compound's drug-likeness

Lipinski's rule / Compound	Molecular weight (<500g/mol)	LogP (<5)	H-bond donor (<5)	H-bond acceptor (<10)
Niazimicin	357,12	1.452	4	6
tert-Butyl 4-(5-formyl-2-thienyl)piperazine-1-carboxylate	296,12	2,004	0	5
Sialic acid	309,11	-3,525	7	10
Fucose	164,07	-0,994	4	5

5.0 CONCLUSION

This study proved that niazimicin has greater potential as a glycosiltransferase inhibitor than other existing inhibitors based on its binding afinity and intermolecular interactions. Niazimicin is a potential anticancer drug according to Lipinski's rule.

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