VIRTUAL SCREENING COMPOUNDS IN FABACEAE PLANTS AS LIGANDS ON ALPHA ESTROGEN RECEPTOR (ER-α)

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ABSTRACT
Family Fabaceae has about 730 genera and 19,400 species. Some plant of family Fabaceae are known to have activity as an anti-breast cancer. This study does a series of computational chemistry method in virtual or in silico screening to compounds in the plant of family Fabaceae that are Abrus schimperi, Caesalpinia bonduc, Dalbergia vacciniiifolia, Eriosema robustum, Erythrina falcata, Flemingia macrophylla, Genista saharae, Trifolium pratense L., Pachyrhizus erosus and Pisum sativum. The aim of this study is to find candidates of compounds as active ligands on estrogen receptor alpha (ER-α) by in silico and elucidating the amino acids contained in the binding site of compounds by using virtual screening. This protocol uses operating system LINUX Ubuntu LTS 14.04 with integrated applications such as SPORES, PLANTS 1.2, BKChem, Open Babel, R Computational Statistics and PyMOL, ZINC 01914469 as comparator compound, 4-[4-hydroxy-3-(prop-2-en-1-yl) phenyl]-2-(prop-2-en-1-yl) as reference compound and 4-hydroxytamoksifen as positive control. The results of virtual screening conducted on 60 compounds from ten plant of family Fabaceae obtained 24 compounds are actively in the binding pocket of ER-α. The important amino acids to affinity compounds with estrogen receptor alpha (ER-α) is GLU353, ARG394, ASP351 and THR347.

Key words: Fabaceae, Virtual Screening, Estrogen Receptor Alpha (ER-α).

INTRODUCTION
In an era new drug design, drug plants were interested as materials of new drug design. One of strategy to developing molecule design a new drug is utilization of computational chemistry methods by virtual screening or in silico screening. Virtual screening can be reduced, cost and time can be more efficient (Huang, et al., 2006). This study does a series of virtual screening to compounds in the plant of family Fabaceae. Isoflavonoid was contained in family Fabaceae has known as antibrust cancer (Molares and Ladio, 2012). The most of breast cancers are selective on estrogen receptor alpha (ER-α). The important of breast cancer treatment is to inhibit the activity of estrogen on estrogen receptor alpha (ER-α). In this study using virtual screening validated Anita et al (2012) protocol. The protocol used to identify ligands can be active on estrogen receptor.
MATERIALS

Tools:
Hardware: A computer TOSHIBA with processor Intel(R) Core(TM) i5-4200M CPU @ 2.50GHz, NVIDIA 2GB, RAM 4GB, HDD 750GB.

Software: LINUX Ubuntu operating system (version 14.04), screening virtual applications (SPORES, PLANTS, BKChem, Open Babel, PyMOL), Statistical analysis application R i386 3.1.3

Materials:
The 2D structure of compounds from Abrus schimperi, Caesalpinia bonduc, Dalbergia vacciniifolia, Eriosema robustum, Erythrina falcata, Flemingia macrophylla, Genista saharae, Trifolium pratense L., Pachyrhizus erosus, Pissum sativum and DNP (Dictionary of Natural Products, 2015), which is used as a test compounds. BKChem application for drawing the structure of the test compound in the form of 2-dimensional (2D), and then converted by using applications Open Babel. Ligands and receptors were prepared using Spores application. PLANTS application is used to simulate the docking of test compound to ER-α at least 3 times replication. Virtual screening results were analyzed using a statistical test one-tailed paired t-test (to see the match data between pairs of samples tested). PyMOL application used to display the active compounds representative of the test compound in the form of three-dimensional (3D) and the elucidation of amino acids in the binding pocket of ER-α.

RESULTS

Table 1. Compounds Score and In Silico Activity

<table>
<thead>
<tr>
<th>No</th>
<th>Compound</th>
<th>Score Chem PLP ± SD</th>
<th>p-value</th>
<th>Ligand activity as estrogen receptor alfa (ER-α) (in silico)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Caesalpinia bonduc</td>
<td>-87.6484 ± 0.3821</td>
<td>0.9989</td>
<td>Active</td>
</tr>
<tr>
<td>2.</td>
<td>Dalbergia vacciniifolia</td>
<td>-92.2499 ± 1.8347</td>
<td>0.9949</td>
<td>Active</td>
</tr>
<tr>
<td>3.</td>
<td>Eriosema robustum</td>
<td>-92.4449 ± 0.5732</td>
<td>0.9953</td>
<td>Active</td>
</tr>
</tbody>
</table>

METHODS

This study using a protocol of screening virtual validated Anita et al. (2012), for the screening virtual in silico compounds in the plant of family Fabaceae that areAbrus schimperi, Caesalpinia bonduc, Dalbergia vacciniifolia, Eriosema robustum, Erythrina falcata, Flemingia macrophylla, Genista saharae, Trifolium pratense L., Pachyrhizus erosus, Pissum sativum and DNP (Dictionary of Natural Products, 2015), which is used as a test compounds. BKChem application for drawing the structure of the test compound in the form of 2-dimensional (2D), and then converted by using applications Open Babel. Ligands and receptors were prepared using Spores application. PLANTS application is used to simulate the docking of test compound to ER-α at least 3 times replication. Virtual screening results were analyzed using a statistical test one-tailed paired t-test (to see the match data between pairs of samples tested). PyMOL application used to display the active compounds representative of the test compound in the form of three-dimensional (3D) and the elucidation of amino acids in the binding pocket of ER-α.
**Pentanoic acid.** A representative inaktive compound from *Erythrina falcata* plants visualized 3D and showed the compound position in binding pocket ER-α.

**DISCUSSION**

Based on the score Chem PLP from the docking simulation of 60 compounds in...
the plants of family Fabaceae with using reference ligand 4-[4-hydroxy-3-(prop-2-en-1-yl) phenyl]-2-(prop-2-en-1-yl) (dimer compound number 11) obtained 24 active compounds (Table.1) on binding pocket ER-α by in silico.

Figure A and B is a 3D visualized from active and inactive representative compounds using PyMOL application. The compounds were elucidated using PyMOL to explore some active amino acid residues.

CONCLUSION

1. The results of virtual screening conducted on 60 compounds from ten plant of family Fabaceae obtained 24 compounds be active compounds in the binding pocket of ER-α.

2. The important amino acids to affinity compounds with the protein that is GLU353, ARG394, ASP351 and THR347.

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