



IN SILICO SCREENING OF CHEMICAL COMPOUNDS FROM SWEET FLAG (*ARACUS CALAMUS L*) AS α -GLUCOSIDASE INHIBITOR

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ABSTRACT

Research have been conducted screening in silico chemical compound inhibitor α -glucosidase from plants dringo (*Acorus calamus L*) based on the binding site (binding site) are owned by some of the compounds obtained respectively from the inhibition of enzyme / receptor (docking) using the program Argus Lab. Model of the enzyme α -glucosidase was obtained through the protein data bank with the code **1lwj** in the download NCBI website. Models of chemical compounds contained in dringo (*A. Calamus L*) obtained through the site Take out "jamu" Knapsack and made in the formula structures of 2D and 3D using the program ACD / Chemscketch.

Docking results showed activity in the compound 1-ethenyl-1-methyl-2,4-at (prop-1-en-2-yl) Cyclohexane with free energy - 8.04385 kcal / mol, and the compound Isocaesitol with a free energy - 8.28388 kcal / mol.

Keywords: *Acorus calamus L*, Dringo, α Glukosidase inhibitor, In silico

INTRODUCTION

Increasing costs of drug development and reduced number of new chemical entities have been a growing concern for new drug development in recent years. A number of potential reasons for this outcome have been considered. One of them is a general perception that applied sciences have not kept pace with the advances of basic sciences. Therefore, there is a need for the use of alternative tools to get answers on efficacy and safety faster, with more certainty and at lower cost. One such alternative tool is the in silico drug design or the computer aided drug design (CADD). In silico drug design can play a significant role in all stages of drug development from the preclinical discovery stage to late stage clinical development. Its use in drug development helps in selecting only a potent lead molecule and may thus prevent the late stage clinical failures; thereby a significant reduction in cost can be achieved¹. In 2001 Pharmaceutical research and manufacturers of America (PhRMA) estimated the cost at US\$802 million over a period of 11 years from the initial research stage to the successful marketing of a new drug. More recent estimates by DiMasi at the Tufts Center for Study of Drug Development (CSDD) that was published in 2003 put the average cost at US\$802 million spread over 12 years, while the Boston Consulting Group estimates the cost as \$880 million over 15 years⁶. At present the cost involved in the drug discovery process ranges from \$800 million to \$1.8 billion. These estimates are averages and there is significant variation in both time and cost, depending on the nature of the disease being targeted, the type of drug being developed and the nature and scope of the clinical trials required to gain regulatory approval¹. Rhizome of *Acorus calamus L*. (tribe Acoraceae), thousands of years ago has been used in Indian and Chinese medicine system, the plant is very useful in the treatment of central nervous system (CNS) abnormalities. In addition, many traditionally used in

the United States and China to treat diabetes, as well as the Banten used to treat the same disease. Ethyl acetate extract of the rhizome *A. calamus L*. improve insulin secretory sustainable cell (cell line) HIT-T15. The results of in vivo studies on the extract (400 and 800 mg / kg) significantly lowered serum levels of blood glucose during fasting and suppress an increase in blood sugar levels after glucose administration in mice 2g/kg². Research Hao (et al., 2007) found the potential activity of ethyl acetate extract of *A. calamus L*. Improving insulin sensitivity significantly as rosiglitazone (comparative medicine). Hao said that the fraction of ethyl acetate extract of *A. calamus L*. hipolipidemia activity and has other useful effects based mechanism to insulin stimulation. This suggests *A. calamus L*. has the potential to be used in the treatment of diabetes and cardiovascular complications in patients who are not overweight³. Research May (et al., 2010) on the fraction of ethyl acetate extract of *A. calamus L* showed inhibitory activity against α -glucosidase with IC₅₀ 0.41 mg / mL and 100 mg / kg of the extract is clearly reduce elevated blood glucose levels following administration of 5 g / kg of starch in normal mice². Based on what has been stated previously, the research for screening in silico of the active compounds from plant *A. calamus L*. as α -glucosidase inhibitor used Argus Lab program.

RESEARCH METHOD

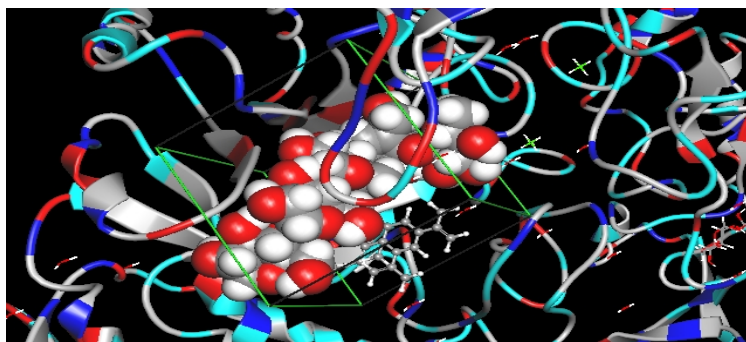
Model of the enzyme α -glucosidase was obtained through the protein data bank with the code **1lwj** in the download NCBI website. Models of chemical compounds contained in dringo (*A. Calamus L*) obtained through the site Take out "jamu" Knapsack⁴ and made in the formula structures of 2D and 3D using the program ACD / Chemscketch. Then docking used Argus lab.

RESULT

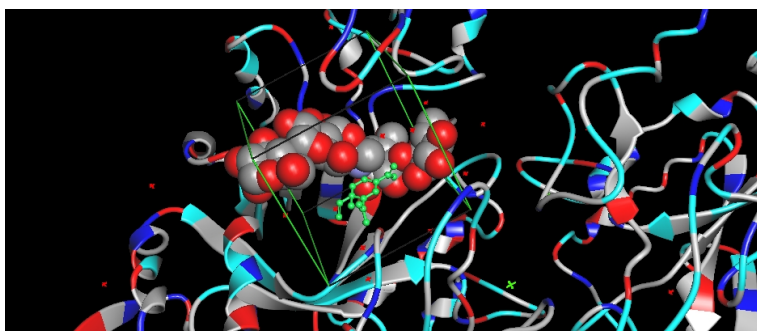
Table 1: Docking result between ligand with the receptor α -glucosidase

No	Ligan / chemical compound	Receptor α -Glucosidase	Free energy (ΔH)	Information
1.	(-)-Cadala-1,4,9-triene	α -Glucosidase	0	(-)
2.	Acolamone	α -Glucosidase	0	(-)
3.	Acoradin	α -Glucosidase	0	(-)
4.	Acoragenmacrone	α -Glucosidase	0	(-)
5.	Acorenon	α -Glucosidase	0	(-)
6.	Acorid acid	α -Glucosidase	-7,26053 kcal/mol	(+)
7.	Acorenene	α -Glucosidase	0	(-)
8.	Aristolene	α -Glucosidase	0	(-)
9.	Beta - acarone	α -Glucosidase	-7,62818 kcal/mol	(+)
10.	Beta - Guanine	α -Glucosidase	0	(-)
11.	Calacone	α -Glucosidase	-7,65883 kcal/mol	(+)
12.	Calamusenone	α -Glucosidase	0	(-)
13.	Calarene	α -Glucosidase	-2,9378 kcal/mol	(+)
14.	1-ethenyl-1-methyl-2,4-di(prop-1-en-2-yl)cyclohexane	α -Glucosidase	-8,04385 kcal/mol	(+)
15.	Delta - cadienene	α -Glucosidase	0	(-)
16.	Apihyobunon	α -Glucosidase	-7,74775 kcal/mol	(+)
17.	Isoacolamone	α -Glucosidase	0	(-)
18.	Isocaespitol	α -Glucosidase	-8,28388 kcal/mol	(+)
19.	Isocalamendiol	α -Glucosidase	0	(-)
20.	Isoshyobunon	α -Glucosidase	0	(-)
21.	Methylsoegenol	α -Glucosidase	-7,92367 kcal/mol	(+)
22.	Preisocalamendiol	α -Glucosidase	0	(-)
23.	Shyobunon	α -Glucosidase	-7,75501 kcal/mol	(+)

(-) : Not activ as α -Glucosidase inhibitor
 (+) activ as α -Glucosidase inhibitor



Picture 1: 1-ethenyl-1-methyl-2,4-di(prop-1-en-2-yl)cyclohexane



Picture 2 : Isocaespitol

DISCUSSION

Recently, *In silico* has play an important role in drug design and discovery. In which small molecule are virtually docked into drug target and the binding affinities are estimated using simplified free energy calculation method.

Many programs capable of carrying out virtual screening have been developed, most of them are payware. One, freely available docking software package potentially capable is ArgusLab. Argus lab was originally developed as molecular modeling software. It provides users with molecular building analyses, the ability to perform various molecular calculation and molecular structure visualization capabilities. Molecular

docking analysis capability was added to latest version of ArgusLab(ver.4.0.1). ArgusLab can be easily used even by beginner in computational docking and can run using windows (Microsoft Corp).

The enzyme α -glucosidase is the enzyme responsible for the conversion of carbohydrates into glucose. Carbohydrates are digested by enzymes in the mouth and intestines into simpler sugars which will then be absorbed into the body and improve blood sugar⁵.

Model of the enzyme α -glucosidase was obtained through the Protein Data Bank (PDB) with code that 1lwj download from the NCBI site. Models of chemical compounds contained in

AC obtained several compounds such as *Beta asarone*, *Acoradine*, *Methylsoegenol*, *1-ethenyl-1-methyl-2,4-di(prop-1-en-2-yl)cyclohexane*, *Isocaespitol*, *Acoragermacrone*, *Preisocalamendiol*, *Shyobunon*, *Epishyobunone*, *Isocalamone*, *Acolamone*, *Aristolene*, *(-)-Cadala-1,4,9-triene*, *Isocalamendiol*, *Calacone*, *Beta-gualene*, *Calamusenon*, *Acoronene*, *Acorid acid*, *Calarene*, *Acorenone* through the site Take out "jamu" Knapsack and made in the formula structures of 2D and 3D using the program ACD / Chemscketch. Then docking used Argus lab Program are visualized by Pymol program.

Docking results showed activity in the compound 1-ethenyl-1-methyl-2,4-at (prop-1-en-2-yl) Cyclohexane with free energy - 8.04385 kcal / mol, and the compound Isocaespitol with a free energy - 8.28388 kcal / mol. Chemical component that has the lowest free energy showed the most stable affinity that is expected to have good medicinal properties as well.

CONCLUSION

Docking results showed activity in the compound 1-ethenyl-1-methyl-2,4-at (prop-1-en-2-yl) Cyclohexane with free

energy - 8.04385 kcal / mol, and the compound Isocaespitol with a free energy - 8.28388 kcal / mol.

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