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In Silico Screening of Chemical Compound Activity as an α-Glucosidase Inhibitor from Sweet Flag Rhizome (*Acorus calamus* L.)

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Abstract
The research on screening in silico of the chemical of *Acorus calamus* L. as an inhibitor of α-glucosidase has been conducted. This research aims to obtain an active chemical compound towards *Acorus calamus* L., which is potentially be inhibitor of α-glucosidase using the screening method in silico. The docking process was employed using 28 chemical compounds in the *Acorus calamus* L. as the ligand to the inhibitor α-glucosidase, becoming the target receptor using PyRx and ArgusLab programs. The chemical compound model of *Acorus calamus* L was obtained from Take Out "Jamu" KnapSack. Whereas the enzyme model of α-glucosidase was obtained from the Protein Data Bank (PDB) with the enzyme code ILWJ. Each compound, which has been docked using enzyme α-glucosidase taken from the free energy changing ΔG as the docking result, and the visualization of the docking result was conducted using the PyMol program. The evaluation result of AG indicated that 28 chemical compounds of Acarus calamus have potential as inhibitors of α-glucosidase, where Delta-Cardinene, with the lowest change, had the most potential. The approximate free energy change (ΔG) was -8.50 kcal/mol in the PyRx and -9.53 kcal/mol in the ArgusLab program.

I. Introduction

In the early stages of developing new drugs, the process is typically based on trial and error, which makes drug development extremely costly (Ruesgas-Ramón, Figueroa-Espinoza and Durand, 2017). This high expense arises because, out of 8,000 to 10,000 new compounds synthesized or derived from natural sources, only one may eventually be approved for clinical use after extensive testing (Wu *et al.*, 2017). These tests include chemical, physical, biological activity, toxicity, pharmacokinetics, pharmacodynamics, and clinical trials. The entire journey from synthesis or extraction to pharmacological screening, clinical evaluation, and regulatory approval requires considerable time (Chunarkar-Patil *et al.*, 2024).

The process takes roughly 10 years, largely because of the stringent regulations governing new drug approvals for market entry (Michaeli *et al.*, 2024). To make new drug development economically viable, a transformative approach is needed—one that focuses on conducting research with a carefully chosen set of compounds and on designing these compounds effectively (Vijayalakshmi *et al.*, 2023).

The challenge of limited new drug development is being addressed with the use of computational drug discovery techniques (Tiwari *et al.*, 2023). This computer-assisted design, known as *in silico* methods, significantly accelerates the drug discovery process by identifying drug targets through bioinformatics tools (Askari, Ghofrani and Taherdoost, 2023). Various *in silico* approaches can suggest potential analog compounds and derivatives, including those from natural sources, that may be suitable for synthesis, further development, or as new compound series (Hassan *et al.*, 2024).

The use of *in silico* methods can also be applied to analyze the structure of target macromolecules that may bind to active sites, dock molecules to targets, and much more (Sahu *et al.*, 2024). The rhizome of *Acorus calamus* L. (family Acoraceae) has been traditionally used for thousands of years in America and China to treat diabetes, and similarly, people in Banten have used it for the same purpose (Muslichah *et al.*, 2022).

Scientific data on the dringo rhizome support this; a study by found that the ethyl acetate fraction of *Acorus calamus* L (Muslichah *et al.*, 2022). extract exhibited alpha-glucosidase inhibitory activity, with an IC_{50} of 0.41 µg/mL, and a dose of 100 mg/kg significantly reduced blood glucose spikes in normal mice after administering 5 g/kg of starch (Qamar *et al.*, 2023).

Based on these findings, this study conducts an *in-silico* screening to identify compounds in the rhizome of *Acorus calamus* L. with potential as alpha-glucosidase inhibitors, using the PyRx and ArgusLab software programs.

II. Research Method

II.1 Sample Collection

This study used the enzyme alpha-glucosidase model from the Protein Data Bank (PDB) with the enzyme code 1LWJ, along with chemical compounds from the rhizome of *Acorus calamus* L. These compounds were downloaded from the Take Out "Jamu" Knapsack database in 3D MDL Molfile [V200] (*.mol) format (Tahir, Baharuddin and Najib, 2023).

II.2 Docking Method

The chemical compounds from the *Acorus calamus* L. rhizome were converted from 2D to 3D format using the Chemdisk software, and further optimized with the VegaZZ program. Docking was performed using PyRx and ArgusLab software, with visualizations produced by PyMol (Dewi, Mursalin and Najib, 2013).

II.3 Data Analysis

The study analyzed alpha-glucosidase inhibitor compounds from the rhizome of *Acorus calamus* L., focusing on the ΔG values obtained from docking results via in silico screening using PyRx and ArgusLab, with visualization through PyMol. Gibbs free energy (ΔG) from the docking simulation was used to measure binding energy between the ligand and receptor, where a lower ΔG value indicates stronger binding affinity between the ligand and receptor.

III. Results and Discussion

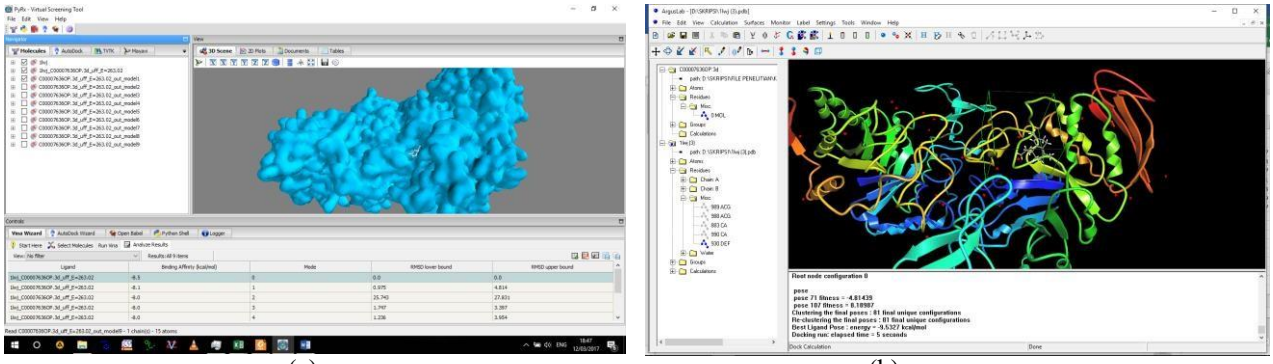
The development of new drugs is rapidly advancing alongside technological progress, notably through the use of computational systems for in silico screening. In silico screening refers to computational systems or analogs that are utilized in biological screening processes. The goal of in silico screening is to evaluate, rank, or filter structural data of a cell using one or more computational methods. This approach assists in identifying compounds for screening or aids in the synthesis process.

Table 1. Docking Results Using PyRx and ArgusLab

No.	Compounds	ΔG (kcal/mol) Docking PyRx	Docking PyRx	ΔG (kcal/mol) Docking ArgusLab	Docking ArgusLab
1.	Eugenol	-6.3	(+)	-8.26727	(+)
2.	Acoradin	-6.9	(+)	-6.70413	(+)
3.	(+)- Champor	-6.7	(+)	-6.76407	(+)
4.	Beta-Asarone	-6.2	(+)	-6.75591	(+)
5.	Curcumin	-7.9	(+)	-8.87543	(+)
6.	Methylisoeugenol	-6.6	(+)	-7.37879	(+)
7.	Cyclohexane	-7.9	(+)	-8.73884	(+)
8.	Delta-Candinene	-8.5	(+)	-9.5327	(+)
9.	Isocaespitol	-7.8	(+)	-7.84004	(+)
10.	Acoragermacrone	-8.9	(+)	-7.32989	(+)
11.	Preisocalamendiol	-8.1	(+)	-8.84415	(+)
12.	Shyobunon	-7.4	(+)	-9.73807	(+)
13.	Epishyobunone	-7.5	(+)	-9.58583	(+)
14.	Isoshyobunone	-7.9	(+)	-8.15675	(+)
15.	Isoacolamone	-8.2	(+)	-8.94841	(+)
16.	Acolamone	-8.3	(+)	-9.04834	(+)
17.	Aristolene	-8.3	(+)	-7.87859	(+)
18.	(-)-Cadala-1,4,9 Triene	-8.3	(+)	-8.73855	(+)
19.	Isocalamendiol	-8.6	(+)	0	(-)
20.	Calacone	-7.1	(+)	-8.48682	(+)
21.	Beta-Guaiene	-8.2	(+)	-8.27559	(+)
22.	Calamusenone	-8.8	(+)	-7.61711	(+)

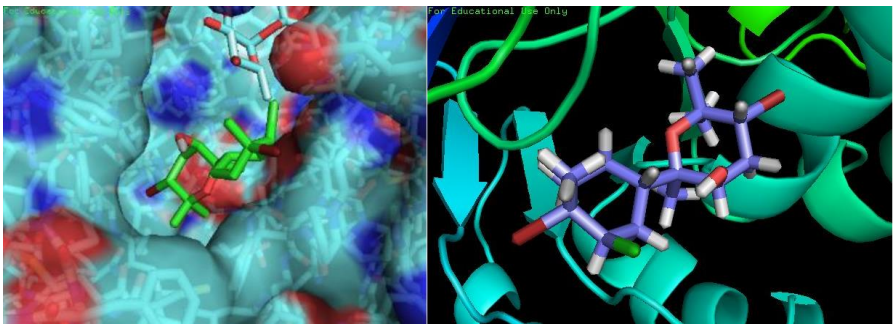
23.	Acoronene	-8.2	(+)	-7.42828	(+)
24.	Acoric acid	-7.4	(+)	-7.34594	(+)
25.	Calarene	-8.6	(+)	-8.4663	(+)
26.	Acorenone	-8.1	(+)	-8.94732	(+)
27.	Cis-Methyl Isogenol	-6.2	(+)	-7.36853	(+)
28.	Isosinomenine	-8.3	(+)	-7.08711	(+)

Note : (+) Inhibit; (-) Non Inhibit



(a) (b)

Figure 1. Docking results of the Delta-cadinene compound using (a) PyRx and (b) ArgusLab



(a) (b)

Figure 2. PyMol visualization of the docking results for the delta-cadinene compound using (a) PyRx and (b) ArgusLab

Numerous programs (applications) are available for virtual screening, both paid and free. Among these are applications like PyRx, ArgusLab, and AutoDock Molegro, which are commonly used for the docking modeling of various compounds with targeted enzymes or receptors. α-glucosidase is an enzyme responsible for converting carbohydrates into glucose. It transforms carbohydrates in the mouth and intestines into simple sugars, which are then absorbed into the body, leading to an increase in blood sugar levels. The model of the α-glucosidase enzyme was obtained (downloaded) from the official NCBI Protein Data Bank (PDB) under code 1LWJ.

The chemical compounds found in *Acorus calamus* L. include Eugenol, Acoradin, (+)-Camphor, beta-Asarone, Curcumin, Methylisoeugenol, Cyclohexane, Delta Cadinene, Isocaespitol, Acoragermacrone, Isoshyobunone, Isoacolamone, Aristolene, (-)-Cadala-1,4,9-triene, Isocalamendiol, Calamusenone, Acoronene, Acoric acid, Calarene, Acorenone, cis-Methyl isoeugenol, and isosinomenine (Table 1). These compounds were obtained (downloaded) from the "Jamu" Knapsack website, and their structures were converted from 2D to 3D using the ACD/ChemSketch program. Docking was performed using PyRx (Figure 1) and ArgusLab, followed by visualization with PyMol (Figure 2).

From the docking results, the evaluation of the changes in free energy (ΔG) indicated that the compound Delta Cadinene exhibited the lowest free energy (ΔG) values according to both programs used (PyRx and ArgusLab). The values were -8.5 kcal/mol in PyRx and -9.5327 kcal/mol in ArgusLab (Table 1). This low free energy suggests that the compound has a good affinity, and it is expected to have beneficial properties as well.

IV. Conclusions

The docking results indicate that the chemical compound with alpha-glucosidase inhibitory activity is Delta Cadinene, which has

free energy (ΔG) values of -8.5 kcal/mol in the PyRx program and -9.5327 kcal/mol.

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