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α-Glucosidase Enzyme Inhibitory Activity of Extracts from the Fermentation of Endophytic Bacteria from Periwinkle (*Catharanthus roseus* (L.) G. Don) Leaves

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Abstract: *Catharanthus roseus* (L.) G. Don contain bioactive compounds that act as inhibitors against the α-glucosidase enzyme. This study aims to test the α-glucosidase enzyme inhibitor activity of fermented extract of endophytic bacteria from tapak dara leaves and identify the bacterial species. Endophytic bacteria were isolated using a direct planting method, resulting in eight isolates. The bacteria were fermented for 24-72 hours in nutrient broth media. Ethyl acetate was used to extract the fermented bacteria. Screening for α-glucosidase enzyme inhibitory activity was conducted using the TLC bioautography method. Four bacterial isolates (TD 1, TD 3, TD 4, TD 7) produced clear zones, qualitatively indicating that the isolates have inhibitory activity against the α-glucosidase enzyme. The IC_{50} results from the eight isolates showed that three isolates provided strong IC_{50} values: isolate TD 1 at 19.93 µg/ml, isolate TD 2 at 92.34 µg/ml, and isolate TD 4 at 13.94 µg/ml, compared to acarbose at 48.85 µg/ml). Molecular identification showed that isolate TD 1 was *Pseudomonas oryzihabitans* and isolate TD 4 was *Staphylococcus warneri*. This study concluded that endophytic bacteria from tapak dara leaves have the potential as a source of α-glucosidase enzyme inhibitor compounds for the development of antidiabetic drugs.

Keywords: α-Glucosidase enzyme inhibitor; Bioautography; Endophytic bacteria; (*Catharanthus roseus* (L.) G. Don); IC_{50}

Introduction

Diabetes mellitus is a metabolic disorder that occurs due to the inability of the pancreas to produce insulin normally (Faridah et al., 2022; Najim et al., 2024; Nguyen et al., 2024). This condition is divided into two main types, namely type 1 diabetes, which is caused by an autoimmune reaction against pancreatic beta cells, and type 2 diabetes, which is caused by insulin resistance, so that the insulin produced cannot function effectively (Hati et al., 2023; Narasukma et al., 2021; Prasetyastuti & Ghozali, 2021). Type 2 diabetes is the most common type and is closely related to modern unhealthy diets and lifestyles (Le et al., 2023; Panduwiguna et al., 2023; Sasongko et al., 2024).

α-glucosidase inhibitors are one group of antidiabetic drugs used to manage blood sugar levels in patients with type 2 diabetes (Nilamsari et al., 2023; Pawestri et al., 2021; Wahyuni et al., 2024). These drugs work by inhibiting the α-glucosidase enzyme which plays a role in hydrolyzing complex carbohydrates into simple sugars (Atmaja et al., 2023; Wati et al., 2024; Hariyadi et al., 2023). One of the commercialized inhibitors, acarbose, is isolated from Actinobacteria, but its use often causes side effects such as gastrointestinal and liver disorders, as well as symptoms of toxicity

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(Agustina et al., 2024; Malothu et al., 2024.; Subandi et al., 2024). Therefore, alternatives from natural materials that are safer but still effective are needed (Ali et al., 2023; Atikana et al., 2023; Khalid et al., 2023).

Endophytic microbes, which live in plant tissues without causing adverse effects on their host, have been recognized as a source of bioactive compounds that have pharmaceutical activity (Agustina et al., 2024; Teffo et al., 2024; Zubair et al., 2022). Various secondary metabolites produced by endophytic microbes, such as alkaloids, steroids, terpenoids, phenolics, and flavonoids, make them potential candidates in the development of antidiabetic drugs (Pertiwi et al., 2023; Saepudin et al., 2022; Yudanti et al., 2024). In previous studies, it has been found that endophytic bacteria from *Ficus deltoidea* plants are able to inhibit the α-glucosidase enzyme, showing great potential as bioactive agents for the treatment of diabetes (Azyenela et al., 2023; Faizah et al., 2020; Iswandana et al., 2022).

The tapak dara plant (*Catharanthus roseus* (L.) G. Don) is a medicinal plant that is often used traditionally for the treatment of diabetes in Indonesia. Some studies, such as the one conducted by Arifin et al. (2024) and Hidayat et al., (2023), showed that the methanol extract of tapak dara leaves has a fairly strong α-glucosidase enzyme inhibitory activity, which is 57.78% (Sari et al., 2022). However, research on the potential of endophytic bacteria from tapak dara leaves as α-glucosidase inhibitors is still limited (Barber et al., 2021; Rakhmawatie et al., 2023; Şöhretoğlu et al., 2023).

This study aims to identify the inhibitory activity of α-glucosidase enzyme from fermented extracts of endophytic bacteria of tapak dara leaves (Bahtiar, 2023; Khaerunnisa et al., 2022; Sholihah et al., 2023). In addition, endophytic bacteria that have the best activity will be identified molecularly to determine the species. This study is expected to provide alternative solutions in the treatment of diabetes using natural ingredients that are safer and have minimal side effects.

Method

This research is a laboratory experimental research conducted at the Microbiology Laboratory of the Faculty of Pharmacy and the Sumatra Biota Laboratory, Andalas University, for 6 months. The research stages include isolation and purification of endophytic bacteria from tapak dara (*Catharanthus roseus* L.) leaves, bacterial fermentation to produce bioactive extracts, α-glucosidase enzyme inhibition activity test, determination of IC_{50} values, and molecular identification of bacteria with the best inhibition activity. The tapak dara leaf samples were taken from Limau Manis, Padang, and identified at the Herbarium of the Faculty of Mathematics and Natural Sciences, Andalas University.

The research procedure began with sterilization of the leaf surface using 70% ethanol, 1% sodium hypochlorite, and sterile distilled water. Leaf pieces were planted on Nutrient Agar media and incubated at 37°C for 24-48 hours until colonies of endophytic bacteria appeared. The growing colonies were purified by replanting on the same media, then fermented on Nutrient Broth media for 5-7 days with 150 rpm agitation. The supernatant from the fermentation was extracted using ethyl acetate, then evaporated using a rotary evaporator to obtain a thick extract.

The extracts obtained were tested for α-glucosidase enzyme inhibitory activity using the spectrophotometric method. The substrate p-nitrophenyl-α-D-glucopyranoside (pNPG) was used to measure enzyme activity, with absorbance measured at a wavelength of 405 nm. The percentage inhibition was calculated by comparing the absorbance of the sample with the control. Extracts that showed the best inhibitory activity were further tested to determine the IC_{50} value, which is the concentration that can inhibit 50% of α-glucosidase enzyme activity.

Molecular identification was performed on endophytic bacteria that had the highest inhibitory activity. Bacterial genomic DNA was isolated, then amplified using Polymerase Chain Reaction (PCR) method with 16S rRNA gene target. The amplification results were then sequenced and compared with the sequence database to identify the endophytic bacterial species. Inhibition test data were analyzed to determine the IC_{50} value, while molecular identification results were used to determine the bacterial species with the best inhibition activity.

Result and Discussion

This study successfully isolated three endophytic bacteria from the leaves of tapak dara (Catharanthus roseus L.), coded TD1, TD3, and TD4. These isolates were purified and used for α-glucosidase inhibitor activity test.

Figure 1 shows the pure isolate of endophytic bacteria isolated. The isolate was further fractionated with ethyl acetate solvent and tested for its inhibitory activity using KLT-bioautography method. The results of the bioautographic KLT test are shown in Figure 2, where the KLT plate was observed at various UV wavelengths and using anisaldehyde and α-glucosidase enzyme to detect the inhibition zone.

The α-glucosidase enzyme activity test results showed that TD1 isolate had the highest inhibition activity compared to other isolates, with an IC_{50} value of

19.93 µg/ml (Table 1). This highest inhibition activity is indicated by the clear zone formed on the KLT plate after being reacted with α-glucosidase enzyme and substrate (Figure 2d).

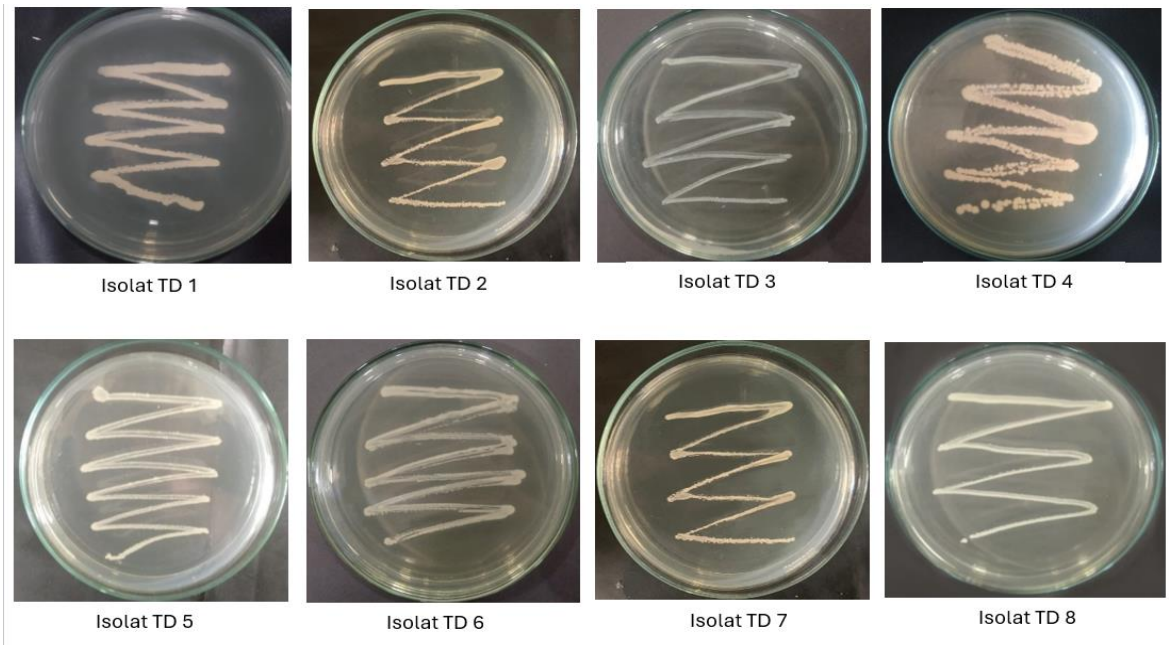

Figure 1. Pure isolate of endophytic bacteria of tapak dara (*Catharanthus roseus* (L.) G. Don) leaves

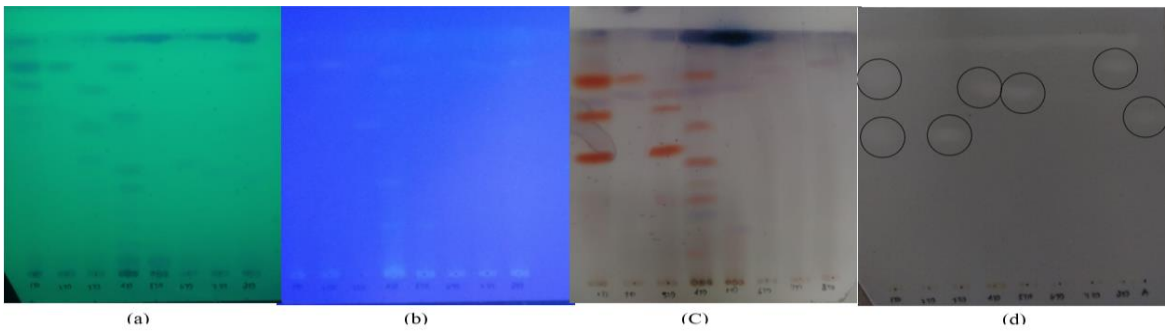

Figure 2. Alpha glucosidase inhibitor activity assay of 8 ethyl acetate extract of endophytic bacteria of tapak dara leaves (*Catharanthus roseus* L.G. Don)) by KLT-bioautography with eluent G (Toluent: Ethyl Acetate: Formic acid = 7;2. 5;0.5) (a) UV 254 nm KLT plate; (b) UV 354 nm KLT plate; (c) KLT plate with anisaldehyde stain (d) KLT plate reacted with alpha glucosidase enzyme, substrate, and Fast blue B salt stain

Table 1. Percent inhibition and IC_{50} of ethyl acetate extract of endophytic bacteria isolate TD 1

Concentration (µG/ml)	A	B	%Inhibition	IC_{50}
200		0.009 ± 0.214	99.38	
100		0.0032 ± 0.097	97.74	
50		0.098 ± 0.054	93.03	
25	1.40	0.138 ± 0.144	90.18	19.93
12.5		0.995 ± 0.984	29.20	
6.25		1.393 ± 1.363	0.92	
3.125		1.578 ± 1.411	-12.210	

Table 2. Percent inhibition and IC_{50} of ethyl acetate extract of endophytic bacteria isolate TD 3

Concentration (µg/ml)	A	B	%Inhibition	IC_{50}
200		0.338 ± 0.438	74.15	
100		0.548 ± 0.587	56.13	
50		0.917 ± 0.949	29.97	
25	1.30	1.162 ± 1.178	11.23	92.34
12.5		1.223 ± 1.243	5.80	
6.25		1.270 ± 1.274	2.95	
3.125		1.295 ± 1.301	1.04	

Table 3. Percent inhibition and IC_{50} of ethyl acetate extract of endophytic bacteria isolate TD 4

Concentration (µg/ml)	A	B	%Inhibition	IC_{50}
200		0.011 ± 0.208	99.13	
100		0.029 ± 0.129	97.83	
50		0.071 ± 0.107	94.57	
25	1.30	0.197 ± 0.213	84.95	13.94
12.05		0.573 ± 0.556	56.25	
06.25		0.975 ± 0.972	25.49	
3.125		1.189 ± 1.183	9.14	

On the other hand, isolates TD3 and TD4 had larger IC_{50} values of 92.34 µg/ml and 13.94 µg/ml, as shown in Table 2 and 3. For comparison, acarbose with an IC_{50} value of 48.85 µg/ml was used (Table 4), indicating that the inhibitory activity of TD1 isolate was higher than that of acarbose, a standard drug for α-glucosidase inhibition.

Molecular identification results show that isolates TD1 and TD4 are different species based on phylogenetic analysis using the neighbor-joining method. Figure 3 and Figure 4 show the phylogenetic tree of isolates TD1 and TD4, where both are included in the group of endophytic bacteria that have the potential to produce bioactive metabolites.

Table 4. Percent inhibition and IC_{50} of acarbose comparator

Concentration (µg/ml)	A	B	%Inhibition	IC_{50}
309.78		0.879 ± 0.259	65.36	
154.89		1.309 ± 0.199	48.40	
77.44		1.370 ± 0.225	46.01	
38.72	2.53	1.703 ± 0.388	32.87	48.85
19.36		2.019 ± 0.166	20.41	
9.68		2.395 ± 0.105	5.61	
4.84		2.400 ± 0.320	5.4	

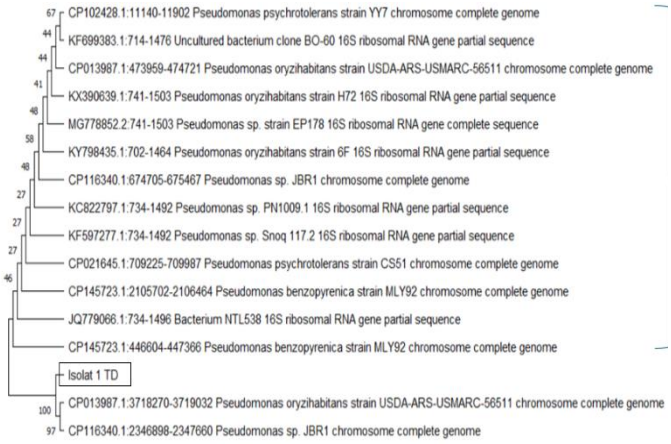

Figure 3. Phylogenic tree inferred by the neightbor-join method from endophytic bacteria TD 1

Figure 4. Phylogenic tree inferred by the neightbor-join method from endophytic bacteria TD 4

This study confirms that tapak dara (*Catharanthus roseus*) leaves are a rich source of endophytic bacteria capable of producing bioactive compounds with α-glucosidase enzyme inhibitory activity. The results of this study indicate that endophytic bacterial extracts from tapak dara leaves, especially isolates TD1 and TD4, have significant potential in α-glucosidase enzyme inhibition, which can be used as an alternative in the therapy of type 2 diabetes mellitus.

Isolate TD1, identified as *Pseudomonas oryzihabitans*, showed the strongest inhibitory activity with an IC_{50} value of 19.93 µg/ml, much more effective than acarbose, a standard inhibitor with an IC_{50} of 48.85 µg/ml. This inhibitory activity is related to the ability of endophytic bacteria to produce secondary metabolites that are able to interfere with the work of the α-glucosidase enzyme, which plays a role in breaking down complex carbohydrates into glucose. Inhibition of this enzyme is crucial in controlling postprandial blood glucose levels, which is often a problem in diabetics (Hasibuan et al., 2023; Hasnawati et al., 2022). In addition, *Pseudomonas oryzihabitans* is also known to have the potential to enhance plant growth, which suggests that this bacterium has a multifunctional role in both agriculture and medical fields (Hikmawati et al., 2021; Parmiti et al., 2021).

Isolate TD4, identified as *Staphylococcus warneri*, also showed good inhibitory activity with an IC_{50} value of 110.56 µg/ml. Although its activity is not as strong as isolate TD1, *Staphylococcus warneri* has the potential to produce bioactive compounds that can act as α-glucosidase enzyme inhibitors. This bacterium has also been known to have good fermentative ability and is able to inhibit the growth of pathogenic microorganisms in certain environments, as found in research on traditional fermented foods.

Screening testing of α-glucosidase enzyme inhibitory activity using the KLT-bioautography

method provides clear visual information regarding the position of active compounds in the ethyl acetate extract of endophytic bacteria. In Figure 2, the clear zone with purple background indicates the inhibition of enzyme activity by the compounds present in the extract. This method was chosen because of its advantages, such as cost efficiency and ease of detection of active compounds, and has been used in various other studies for screening inhibitory enzyme activity. The success of TD1, TD3, TD4, and TD8 isolates in providing clear zones indicates the presence of potential inhibitory compounds contained in the endophytic bacteria of tapak dara leaves.

In a molecular context, the phylogenetic tree construction of isolates TD1 and TD4 revealed a close relationship with other bacterial species, such as *Pseudomonas* sp. and *Staphylococcus* sp., which are also known to have the potential to produce bioactive metabolites. This classification strengthens the understanding of the diversity of endophytic bacteria within a single plant species, indicating that plants such as periwinkle can be a source of bacteria with various beneficial biological potentials.

This study shows that endophytic bacteria from tapak dara leaves have great potential as a source of α-glucosidase enzyme inhibitor compounds, which play an important role in the development of alternative therapies for diabetes mellitus. Further isolation and identification of active compounds from these endophytic bacteria may lead to the development of new drugs that are more effective and safer in overcoming the problem of hyperglycemia in diabetic patients.

Conclusion

This study showed that of the eight endophytic bacterial isolates of tapak dara (*Catharanthus roseus*) leaves, four isolates had α-glucosidase enzyme inhibitory activity, with three isolates (TD1, TD3, and TD4) showing good IC_{50} values. Molecular characterization identified *Pseudomonas oryzihabitans* (isolate TD1) and *Staphylococcus warneri* (isolate TD4) as selected endophytic bacteria with potential as α-glucosidase enzyme inhibitors. Isolate TD1 has the best inhibitory activity with IC_{50} value of 19.93 µg/ml, exceeding acarbose as a comparator. Further research is needed to identify the bioactive compounds involved in this activity and develop its potential as a natural antidiabetic agent.

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Author Contributions
U.RH. designed the experiment, conducted the experiment, provided several resources, analyzed, interpreted the results, and drafted the article. N.A. conducted the experiment and provided resources. V.F.S. conducted the experiment and drafted the article. F.I. analyzed the data. R. designed the research concept and experiment, analyzed the data. All authors contributed to the manuscript, drafting, reading, and revising. The final manuscript has been read and approved by all authors.

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Conflicts of Interest
The authors declare no conflict of interest.

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