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The Potential Of Fungi And Bacteria As α-Glucosidase Inhibitors For The Future Treatment Of Type 2 Diabetes

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Abstract: Diabetes, a disorder of hemostasis of carbohydrate and lipid metabolism, is one of today's leading killers. The most prevalent form of diabetes is type 2 diabetes mellitus (T2DM). Rapid hydrolysis of starch by pancreatic α-amylase and α-glucosidase, followed by intestinal absorption of glucose, causes a sudden increase in blood glucose. Available therapies for T2DM are oral insulin secretagogues, sulfonylureas, repaglinide, nateglinide, biguanides, thiazolidinediones, α-glucosidase, inhibitors and insulin. However, several hypoglycemic agents have limitations, such as side effects and increased diabetes complications. α-glucosidase inhibitors are structurally similar to natural oligosaccharides with a higher affinity for α-glucosidases, and they produce a reversible inhibition of membrane-bound intestinal α-glucoside hydrolase enzymes. This causes delayed carbohydrate absorption and digestion and results in a reduction in postprandial hyperglycemia. Natural α-glucosidase inhibitor drugs from natural sources can be used as a therapeutic approach to treat postprandial hyperglycemia for their assumed lower side effect and more affordable price than synthetic drugs. In this article, the author summarizes the potential of α-glucosidase inhibitors from microorganisms, namely fungi and bacteria, along with several active compounds with better activity than commercial α-glucosidase inhibitors.

Keywords: Bacteria, Endophyte Fungi, α-Glucosidase Inhibitors.

Introduction

Diabetes mellitus is the most common endocrine metabolic disorder, affecting more than 400 million people worldwide, and by 2040 it is estimated that 640 million people will suffer from type 2 diabetes mellitus (T2DM) worldwide (Marín-Peñalver et al., 2016). Chronic hyperglycemia and insulin resistance to target tissues, especially skeletal muscle, adipose tissue, insulin receptors, signal transduction systems, enzymes, and effector genes are caused by defects in insulin secretion, action, or both. Sedentary lifestyles and obesity-causing diets are the main causes of T2DM (Kharroubi, 2015). By 2030, it is estimated there will be an increase in the population suffering from type 2 diabetes mellitus by 69%, especially among adults in the developing countries (Al Mansour, 2020). Type 2 diabetes mellitus is often accompanied by various comorbidities that increase the risk of drug-related problems (DRP). This is due to the complexity of drug therapy given to T2DM patients. Furthermore, this DRP will lead to increased morbidity, expensive medical costs, and even death (Belayneh et al., 2021). Currently available therapies for T2DM are as follows oral insulin secretagogues,

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sulfonylureas, repaglinide, nateglinide, biguanides, thiazolidinediones, α-glucosidase inhibitors, insulin, pramlintide, exenatide (Akram, 2013). However, several hypoglycemic agents have limitations, such as adverse effects and increased diabetes complications. Bloating, nausea, and diarrhea are the main adverse effects of α-glucosidase in the gastrointestinal tract. Oral hypoglycemic agents (OHAs) are the most common drugs in T2DM which have various adverse effects related to their use, including hypoglycemia, weight gain, gastrointestinal disturbance, lactic acidosis, and fluid retention (Shrestha et al., 2017). Insulin has been reported to have allergic side effects, weight gain, and lipodystrophy. Acarbose, an α-glucosidase inhibitor, has been reported to have gastrointestinal side effects and hepatitis. Intestine α-glucosidase inhibitors, comparable to natural oligosaccharides, have a higher affinity for the enzymes and inhibit membrane-bound intestine α-glucoside hydrolases temporarily. This delays carbohydrate digestion and reduces postprandial hyperglycemia. Due to lower blood glucose levels, α-glucosidase inhibitors do not increase insulin secretion (He et al., 2014; Osadebe et al., 2014).

Thiazolidinedhione (TZD) and metformin are two available drugs that have been used in T2DM treatment recently. However, both drugs may cause serious adverse effects to some specific patients. Renal function loss, concurrent liver disease or excessive alcohol consumption, unstable or acute heart failure, and a personal history of lactic acidosis are all risk factors. The most common are gastrointestinal symptoms such as anorexia, nausea, abdominal discomfort, and diarrhea, which are usually minor and transitory. Metformin also lowers vitamin B12 absorption in the intestine and possesses lipid-lowering properties, resulting in a reduction in free fatty acid concentration, serum triglyceride, a moderate drop in LDL cholesterol, and a modest increase in HDL cholesterol (Ghosal, 2019; Marín-Peñalver et al., 2016; Nasri & Rafieian-Kopaei, 2014).

Natural α-glucosidase inhibitor drugs from natural sources can be used as a therapeutic approach to treat postprandial hyperglycemia for their assumed lower side effect and more affordable price than synthetic drugs (Munasaroh et al., 2018). Various medicinal plants have been investigated for their hypoglycemic effect. Some of them showed promising activity in vivo or in vitro experiments. On the other hand, the exploration of medicinal plants as raw materials to produce mass natural drug substances would decrease natural diversity if we exploited too much (Munim et al., 2013). α-glucosidase is an intriguing target enzyme to treat type 2 diabetes, and α-glucosidase inhibitors are considered first-line drugs for T2DM patients. Bacteria and fungi are potential sources of secondary metabolites due to their ease of culture and genetic engineering. Fungi, in general, produce natural products with incredible chemical diversity, and many fungal metabolites have illustrated a wide range of biological and pharmacological effects. In this review, the focus is on describing the α-glucosidase effects and their potential as antidiabetic agents of various metabolites isolated from fungi and bacteria (Hussain et al., 2021). Microbial conversion may offer another means of obtaining natural with α-glucosidase inhibitor's promising activity, providing an alternative to commercially available inhibitors—such as acarbose, miglitol, and voglibose—which have been reported to cause side effects (Nguyen et al., 2017).

This study is essential because it explores the potential of microbial metabolites as natural α-glucosidase inhibitors, which could offer safer and more sustainable therapeutic alternatives for T2DM management. The aim of this review is to provide a comprehensive overview of the α-glucosidase inhibitory effects and antidiabetic potential of various metabolites isolated from fungi and bacteria, highlighting their advantages over conventional synthetic drugs and their role in reducing the burden of diabetes-related complications.

Method

This review was conducted through a systematic literature search aimed at identifying relevant studies that explore the potential of fungi and bacteria as α-glucosidase inhibitors in the treatment of type 2 diabetes. A comprehensive search strategy was implemented using a combination of search engines and academic databases. The search process involved three primary sources: Google scholar, Scopus and SINTA.

The initial search was conducted using Google Search to gather a broad overview of the topic and to identify gray literature, including open-access reports, scientific articles, and research summaries related to fungi, bacteria, and α-glucosidase inhibitors. The keywords used included "α-glucosidase inhibitors," "bacteria inhibitors," "fungi inhibitors," "α-glucosidase inhibition by bacteria," and "fungi diabetes treatment." This search served as a preliminary phase to ensure that no relevant studies were overlooked and to understand current developments in this research field.

Next, a detailed and focused search was performed using Scopus, a highly respected and widely used academic database. Keywords such as "α-glucosidase inhibitors fungi," "α-glucosidase inhibitors bacteria," "Type 2 diabetes treatment with microorganisms," and "natural α-glucosidase inhibitors" were used. The search was restricted to articles published within the last 10

years, except for article review, to ensure the inclusion of recent and relevant findings. Additionally, to gather studies from Indonesian researchers and local scientific contributions, SINTA, Indonesia's national scientific database, was also utilized. This search aimed to uncover research specific to fungal and bacterial species found in Indonesia that could serve as potential α-glucosidase inhibitors. The search terms used were similar to those applied in Scopus, with an emphasis on studies published in Indonesian journals and databases indexed in SINTA.

Filters were also applied to focus on research articles, reviews, and meta-analyses published in reputable, peer-reviewed journals. Articles identified from all sources were screened based on their titles and abstracts to ensure relevance to the review's scope. Studies were included if they met the following criteria: (1) they investigated fungi or bacteria as α-glucosidase inhibitors; (2) they involved experimental or clinical research on diabetes type 2 treatment using microbial inhibitors; (3) they were published in peer-reviewed journals; and (4) they were available in English or Indonesian. Studies focused solely on synthetic inhibitors or non-microbial natural inhibitors were excluded from this review.

The flowchart of method was showed in Figure 1.

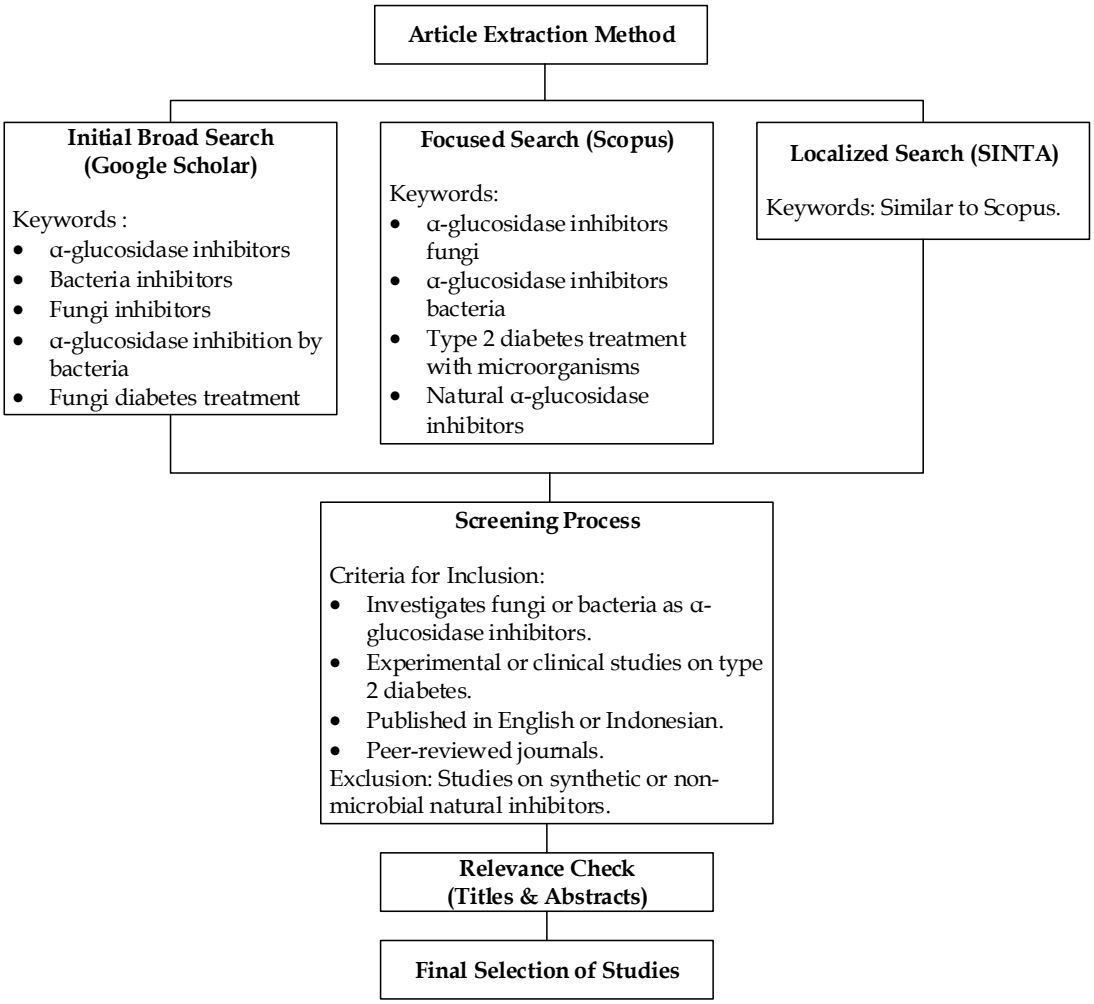

Figure 1. Systematic Literature Review Methodology for Exploring Fungi and Bacteria as α-Glucosidase Inhibitors

Result and Discussion

Mechanism of action of a-glucosidase inhibitors

One of the risk factors is the high post-prandial hyperglycemia (PPHG) caused by rapid hydrolysis of starch by pancreatic α-amylase and α-glucosidase which is followed by intestinal absorption of glucose, triggering a sudden increase in blood glucose. Post-prandial hyperglycemia (PPHG) is known as the plasma glucose value taken 1.5–2 h after a meal (Proença et al., 2017). The action of α-glucosidases elevates PPHG. α-glucosidase inhibitors play a significant role in managing PPHG in diabetic patients. Inhibition of α-glucosidase enzyme activity leads to a reduction in starch hydrolysis, which has beneficial effects on glycemic index control in diabetic patients (Naquvi et al., 2011). Diabetics with PPHG are at risk for vascular problems that cause disability and death. α-glucosidase

inhibitors reduce postprandial glycemic spikes and lower fasting blood glucose by blocking carbohydrate-induced intestinal sugar transport increases. Most likely, sustained hyperglycemia reduction will lessen the risk of microvascular problems (Wresdiyati et al., 2015). Acarbose is the most commonly used drug and the most widely studied one. Acarbose inhibits α-amylase, maltase, sucrase, and dextranase and is most effective against glucoamylase. Acarbose and voglibose (not FDA-approved in the USA) are poorly absorbed from the gut, have low bioavailability, and are excreted in the stool. Miglitol, on the other hand, is absorbed from the gut completely and is excreted through the renal route. Acarbose undergoes metabolism in the colon, while miglitol and voglibose have no metabolites (Manahil & Roopma, 2021). α-glucosidase inhibitors are contraindicated in conditions that can worsen due to excess gas formation in the gut and also in patients either suffering from intestinal obstruction or at risk of intestinal obstruction. Other contraindications include diabetic ketoacidosis, chronic intestinal disease, colonic ulceration, inflammatory bowel disease, and known hypersensitivity to this group of drug (Manahil & Roopma, 2021).

Endophytic Fungi Producing Inhibitor a-glucosidase

Natural products from endophytic fungi have a broad spectrum of biological activity. They can be grouped into several categories; there are alkaloids, steroids, terpenoids, isocoumarins, quinones, phenylpropanoids and lignans, phenol and phenolic acids, aliphatic metabolites, lactones (Ramdanis et al., 2012). Endophytes are also an abundant source of secondary metabolites, especially endophytic fungi (Sudha et al., 2013). Endophytic fungi usually get nutrition and protection from their host plant and promote plant growth by producing certain bioactive substances (Indrianingsih & Tachibana, 2017).

The various natural products produced by endophytic fungi possess unique structures and great bioactivities, representing a large reservoir with enormous potential for exploitation for medicinal, agricultural, and industrial uses (Padhi et al., 2013). Fungi-derived natural products are considered one of the most relevant sources of discovery and molecular diversity for new drugs. They are a valuable source of biological metabolites with wide-ranging applications as antibiotics (Angelini et al., 2022), antifungals (Deshmukh, Gupta, et al., 2018), antiparasitic (Nandinsuren et al., 2016) and anticancer agents (Lichota & Gwozdzinski, 2018). Aqueous extract and methanol of cinnamon bark showed vigorous antioxidant activity, indicated by the IC_{50} value in reducing free radicals of 3.03 µg/mL and 8.38 µg/mL, respectively. These extracts hold antidiabetic activity through inhibition of glucosidase enzyme, each 94,51% and 90,30%, respectively, with extract concentrations of 1,5%. This antidiabetic activity was also shown by its endophytic fungi. Fungal isolate Cb.D6 isolated from leaves had an antidiabetic and antioxidant activity of 94.21% and 90.28%, respectively (Septiana et al., 2019). In the Table 1, we summarize some of the endophytic fungi that have α glucosidase inhibitory activity

Table 1. Endophytic fungi with α-glucosidase inhibitory activity

Endophytic fungi/isolates	Sources	Secondary metabolites or chemical compound	references
Xylariaceae sp. QGS 01	*Quercus gilva* Blume	8-hydroxy-6,7-dimethoxy-3-methylisocoumarine	21
CMM4B	*S.macrophylla* King	flavonoid	19
Mycosphaerella sp SYSU-DZG01	Mangrove	Asperchalasine, epicoccine derivatives	28
Penicillium canescens	*Juniperis polycarpos*	-1,2,3,5,6-pentahydroxy-8-methylxanthone -1,3,5,6-tetrahydroxy-8-methylxanthone	29
Aspergillus awamori	*Acacia nilotica*	peptide	30
Penicillium pimitouense	*Simarouba glauca*	Flavonoid, triterpenes, alkaloids	31
Zasmidium sp strain EM5-10	Mangrove	Tripalmitin	32
Colletotrichum sp	*Taxus Sumatrana*	Fatty acids	33
Talaromyces amestolkiae YX1	Mangrove	Isocoumarins and benzofurans	34
Alternarea destruens	*Calotropis gigantea*	Phenolic	35

From the Table 1, one of the α-glucosidase inhibitors is xanthones. It was reported that the three xanthones (compounds 5, 7, and 11) had IC_{50} values of 38.80 ± 1.01 µM, 32.32 ± 1.01 µM and 75.20 ± 1.02 µM. In one study, it was reported that asperchalasine, a bioactive compound with α-glucosidase inhibitor activity, was isolated from the endophytic fungus *Mycosphaerella* sp., with an IC_{50} value of 17.1 mM (Qiu et al., 2019). The difference in the activity of this α-glucosidase inhibitor is thought to be caused by whether or not a compound is hydroxylated. The more hydroxylated an active compound is thought to cause the more vigorous α-glucosidase inhibitor activity (Malik et al., 2020). Structure-activity relationship

analyses of xanthones as α-glucosidase inhibitors mainly focus on the aromatic rings' pi-system, the molecule's branching, and the number of hydroxyl groups. The increase in the number of aromatic rings, double bonds, or other conjugate structures is believed to enhance the interaction between compounds and the hydrophobicity surface of the enzyme protein, hence enforcing the inhibitory activity. An increase in the number of the hydroxyl groups is favorable for the inhibitory activity because molecular charge transfers among atoms cause the stabilization of the aromatic rings. Increasing hydroxyls will not be essential if other oxygen-containing groups surround the hydroxyls (Zuo et al., 2014). The most effective secondary metabolites in inhibiting α-glucosidase activity are flavonoids because flavonoids have dual activity, namely hypoglycemic and antihyperglycemic activity (Fontana Pereira et al., 2011). Many of the studied flavonoids offer a promising alternative for managing PPHG, presenting an IC_{50} ≤200 µM, much lower than the one found for acarbose (607 ± 56 µM). A study reported that a flavonoid with two catechol groups in A- and B-rings, together with a 3-OH group at C-ring, was the most active, presenting an IC_{50} much lower than the one found for the most widely prescribed α-glucosidase inhibitor, acarbose. It also reported that a flavone without –OH groups could not inhibit α-glucosidase. From the study, the most active flavonoid was A5, which has a 3-OH in the C-ring and presented an IC50 of 54±3 mM. The replacement of the –OH groups of the catechol in the B-ring by –OMe groups decreased the inhibitory activity of the flavonoid (Proença et al., 2017). Another metabolite with more vigorous antidiabetic activity than acarbose was reported by Qi et al. (2020). His research reported that the endophytic fungus from Ginkgo biloba, identified as *Chaetomium globosum* has 12 metabolites with high α-glucosidase inhibitor activity. The first compound is known to have the highest activity, even more potent than acarbose, with an IC_{50} value of 3.0 mM, which is 18 times stronger than acarbose (IC_{50}=54.74mM). This compound is known to have a C11 polyketide skeleton (Qi et al., 2020). In another study, 22 endophytic fungi were isolated from anti-diabetic plants, *Momordica charantia*, and *Trigonella foenum-graceum*. Ethyl acetate extracts of nine endophytic fungi were positive for α-amylase and α- glucosidase inhibitors. Crude extracts of fungal isolates PTFL005 and PTFL006 showed promising inhibition activity on α- amylase with an IC_{50} value of 15.48 and 13.48µg/mL, respectively. The acarbose had 22.38 µg/mL of IC_{50} value for α-amylase at similar experimental conditions. Fungal isolates PTFL006 and PTFL011 were found to have potent α-glucosidase inhibitors with an IC_{50} value of 17.37 and 10.71µg/mL, which was close to the standard acarbose (6.53µg/mL) (Pavithra et al., 2014). Another novel metabolite that has antidiabetic activity was also reported by Ukwatta et al. (2019). The new compound, nigronapthaphenyl, was extracted from the endophytic fungus *Nigrospora sphaerica* isolated from a mangrove plant, *Bruguiera gymnorrhyza*. *Nigronapthaphenyl* showed antibacterial activities against *Bacillus subtilis* TISTR 088 and *Bacillus cereus* TISTR 688 with MIC values of 4 and 2 µg/mL, respectively. This further showed potential anti-inflammatory activity amounting to an IC50 of 6.2 ± 0.5 µM and also α-glucosidase inhibitory activity, with an IC_{50} value of 6.9 ± 0.5 µM (Ukwatta et al., 2019).

Marine Fungi Producing Inhibitor a-glucosidase

Marine-derived fungi are considered to be the potential sources for new and biologically active secondary metabolites as antibiotics, anti inflammatory (Manimegalai et al., 2013), anti bacterial (Handayani et al., 2020), and anti cancer (Deshmukh, Prakash, et al., 2018). Various kinds of organisms from the oceans produce bioactive compounds that have the potential as medicinal raw materials for diabetic, including algae (Sabarianandh et al., 2020), marine sponge (Sivaramakrishnan et al., 2020), marine seaweed (Unnikrishnan et al., 2014), including marine fungi.

Aspergillus flavipes HN4-13, isolated from sediments in the Lianyungang Sea, China, produced a bioactive compound that inhibited α-glucosidase. Three butenolide derivative compounds, namely flavipesolide A-C, and 13 other known compounds, including aspulvinone, monochlorouslochrin, and dihydrogen, showed potent activity. Compounds 4−6 and 9 were non-competitive α-glucosidase inhibitors with Ki/IC_{50} values of 0.43/ 34, 2.1/37, 0.79/19, and 2.8/90 µM, respectively. Compounds 1−3, 8, 10, and 13 are mixed α-glucosidase inhibitors with Ki/IC50 values of (2.5, 19)/44, (3.4, 14)/57, (9.2, 4.7)/95, (6.3, 5.5)/55, (1.4, 0.60)/9.9, and (2.5, 7.2)/33 µM, respectively (IC_{50} 101 µM for acarbose and 79 µM for 1-deoxynojirimycin) (Wang et al., 2016). In another study, it was reported that *Aspergillus* sp. OUCMDZ-1583, isolated from sea sponges from Xisha Island, produced a potent α-glucosidase inhibitor bioactive compound, up to 35 times stronger than acarbose as a positive control. The active compound was identified as 6-O-demethylmonocerin (Kong et al., 2015).

A new tyrosine-derived metabolite, aspergillusol A (4), was isolated on a gram scale, together with a methyl ester of 4-hydroxyphenylpyruvic acid oxime (5) and secalonic acid A, from the marine-derived fungus *Aspergillus aculeatus* CRI323-04. The tetraol in 4 was identified as erythritol by comparison of the 1 H NMR spectrum of its benzoylated derivative with those of benzoylated erythritol (7) and D-threitol (8), as well as by cellulose-based chiral HPLC analysis. Aspergillusol A (4) selectively inhibited R-glucosidase from the yeast

Saccharomyces cerevisiae, but it was inactive toward the R-glucosidase from the bacterium *Bacillus stearothermophilus* (Ingavat et al., 2009) *Penicillium* sp TW58-16 isolated from hydrothermal sediments, in the Kueishantao region of Taiwan, produced novel bioactive compounds, including 2 drimane sesquiterpenes and 6 new polyketide compounds. These compounds have α-glucosidase inhibitor activity in the range of 35 to 91%. Some compounds showed better activity than acarbose (Saravanakumar et al., 2020).

Bacteria Producing Inhibitor a Glucosidase

Bacteria are the source of secondary metabolites because they are easy to culture and genetically engineered. Probiotics are defined as live microorganisms that confer health benefits to the host (Nurhayati et al., 2015; Sharma et al., 2012; Thantsha et al., 2012). Many studies have reported that bioactive compounds produced by Lactic Acid Bacteria (LAB) have activity in inhibiting α-glucosidase. A study reported that lactic acid bacteria isolated from Canna (*Canna edulis*) and Kimpul (*Zanthosoma sagittifolium*) had activity in inhibiting α-glucosidase. Of 8 isolates, GN 8 lactic acid bacteria isolate even showed a percent inhibition of up to 103%, which was much higher than the positive control, acarbose (87%) (Nurhayati et al., 2017). In one study, *Lactobacillus* isolated from sap showed α-glucosidase inhibitor activity in experimental rats induced with alloxan. The mean blood sugar levels after alloxan induction were 374.6, 347.5, 373.2, 348.4. The mean blood sugar levels at P1, P2 and P3 respectively from the first day to the third day were P1 247.2, 225.8, 209.6, P2 was 241.2, 141.8, 99.6 and P3 were 138,8, 112, 84.6 (Fardhani & Aini, 2021).

Endophytic bacteria also have the potential to produce bioactive compounds that inhibit α-glucosidase. Their diversity and specialized habituation make them an exciting field of study in the search for new medicines (Habbu et al., 2014). Bacterial endophytes colonize internal plant tissues and form different associations with plants, such as mutualistic, trophobiotic, commensalism, and symbiotic. Many endophytic organisms belong to bacterial genera commonly present in soil, including *Bacillus, Burkholderia*, and *Pseudomonas* (Nisa et al., 2021). Endophytic bacteria also produce the same active compounds as their host. In one study, it was reported that as many as six isolates of endophytic bacteria isolated from snake fruit (*Salacca edulis*), namely isolates Dt-A, Dt-B, Kt-E, Kt-I, Dm-A1, and Dm-A2 showed α-glucosidase inhibitor activity of 18.03% respectively. , 21.7%, 62.95%, 19.25%, 30.79%, and 6.14% while the activity of 1% acarbose is 2.08%. The isolated bacteria were Dt- A and Dt-B that, represent the genus *Xanthomonas*, Kt-E from the genus *Paenibacillus*, Kt-I from the genus *Bacillus*, Dm-A1 and Dm-A2 from the family Enterobacteriaceae (Susilowati et al., 2019). In the Table 2 we summarize some of the bacteria that have α-glucosidase inhibitory activity.

Table 2. Bacteria with α-glucosidase inhibitory activity

Plant sources	bacteria	Inhibitor activity	references
Tinospora crispa	*Streptomyces olivochromogenes*	11.02%	59
Oryza sativa	*Bacillus amyloliquefaciens* RWL-1	37%	60
Cao Phong Orange	*Streptomyces* sp	68.98%	61
Annona muricata	Isolate DS21	72.22%	62
Datura stramonium L	*Streptomyces* sp. Loyola UGC	65.48%	63
Moringa oleifera	*Nocardia rhamnosiphila*	7.5%	64
Ficus deltoidea	*Streptomyces* spp	66.2%	65
Rhizosphora stylosa	*Bacillus, Streptomyces, Pseudovibrio*	54.5%	66

Some research has revealed that the exopolysaccharides (EPS) generated by LAB may have α-glucosidase inhibitory action (Prete et al., 2021). The principle mechanism of EPS in inhibiting α-glucosidase activity is the same as acarbose acting. EPS on LAB in the digestive tract can bind to the surface of the intestinal mucosa and inhibit the growth of pathogenic bacteria (Fidien et al., 2021).

Mechanism of hypoglycemic and antihyperglycemic activity of bioactive compounds from fungi and bacteria

The relationship between antidiabetics and activities to the total phenol content both show a positive correlation; the higher the antidiabetic and antioxidant activities, the higher the total phenol contents. Phenol compounds have long been known to have antioxidant and antidiabetic abilities. This ability is related to the structure of phenolic compounds composed of hydroxyl groups that bind to aromatic hydrocarbon groups. The hydroxyl group in phenolic compounds has been reported to have the ability to significantly reduce free radicals by donating hydrogen atoms and an electron to a free radical hydroxyl group. The hydroxyl group in the phenolic compound can be effectively bound to the active site of the α-glucosidase enzyme. This bond allows the phenolic compound to donate hydrogen atoms to form hydrogen bonds with the active site of the enzyme in the mechanism of inhibiting the activity of the α-glucosidase (Septiana et al., 2019). Some flavonoids

and polyphenols as well as sugar derivatives were found to be effective on the inhibitory activities of α-glucosidase (Christhudas et al., 2013). The study reported that several types of LAB have metabolites related to short-chain fatty acid (SCFA) metabolism products of the fermentation of polysaccharides by microbes in the intestines. SCFAs function as ligands for specific G-protein coupled receptors (GPCRs) and modulate several gut hormones involved in glucose and energy homeostasis levels, including glucagon-like peptides. Glucagon-like peptide (GLP-1) lowers blood glucose levels during hyperglycemia by stimulating insulin secretion and reducing glucose dependence. This hormone stimulates satiety and delays gastric emptying through a central mechanism, thereby reducing postprandial glucose levels because by inhibiting the action of the α-glucosidase enzyme, it can delay the decomposition of oligosaccharides and disaccharides into monosaccharides so that compounds that can inhibit the action of the α-glucosidase enzyme can be used as oral drugs for type 2 DM patients (Fardhani & Aini, 2021).

Conclusion

Fungi and bacteria are attractive alternative sources of bioactive compounds with potential as antidiabetic agents/drugs. Further exploration of fungi and bacterial-derived bioactive compounds may significantly contribute to the search for antidiabetic drugs that may possess good efficacy, provide sustainability, and benefit economically. Also noteworthy is that the recent advanced technologies, such as genomic sequencing and metabolomics studies of microbes that potentially carry antidiabetic agents, may boost the exploration of antidiabetic drugs in the future.

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Author contribution
EF, as the first author was responsible for conceptualizing the review, conducting the literature search, analyzing the data, and drafting the manuscript. S provided guidance on the overall direction of the review and critically revised the manuscript for important intellectual content. TTN and I contributed significantly by offering expert input on the biochemical and medical aspects of the review, as well as refining the scope and focus of the manuscript. APJ played a crucial role in the review process by providing valuable feedback and suggestions that significantly enhanced the quality of the manuscript. All authors have reviewed and approved the final version of the manuscript and are accountable for all aspects of the work.

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