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Endophytic fungi hosted anti-diabetic medicinal plants as a source of α-Amylase and α-Glucosidase inhibitors

Basant M. Khader[1*], Abdelghafar M. Abu-Elsaoud[1,2], Amira M. G. Darwish[3], Ahmed M. Abdel-Azeem[1,4]

[1] *Botany and Microbiology Department, Faculty of Science, Suez Canal University, Ismailia 41522, Egypt*
[2] *Department of Biology, College of Science, Imam Mohammad Ibn Saud Islamic University (IMSIU), Riyadh, 11623, Kingdom of Saudi Arabia.*
[3]*Food Industry Technology Program, Faculty of Industrial and Energy Technology, Borg Al Arab Technological University (BATU), Alexandria, Egypt.*
[4] *Department of Genetics, Faculty of Natural and Agricultural Sciences, University of the Free State, Bloemfontein 9300, Republic of South Africa.*

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ABSTRACT

Diabetes mellitus (DM) is a chronic disease that occurs when the body cannot produce or use insulin properly. It is considered one of the most prevalent and fastest-growing diseases in the world, expected to affect 693 million adults by 2045. DM can cause mortalities and morbidities, although this is not directly caused by diabetes, persistent hyperglycemia can lead to serious physical consequences such as blindness, kidney failure, heart disease, and peripheral nerve damage. Treatment of these complications includes removing the main symptoms and maintaining good glycemic control. DM continues to put economic and health pressures on individuals and countries and affects the quality of life of patients. It's miles crucial to search for newer and more effective antidiabetic agents with fewer adverse effects in cheaper costs to minimize the current and future burden of diabetes. Recently, endophytic fungi have received a great deal of attention due to their ability to produce secondary metabolites like those of the host plant. This provides an opportunity to cheaply produce therapeutic natural compounds that can overcome diseases such as diabetes. Recent research has focused on thoroughly understanding the role of endophytes and their impact on diabetes. They showed promising results and paved the way for future research to extract and find new bioactive substances with anti-diabetic properties. The current review focuses on the endophytic fungi-hosted anti-diabetic medicinal plants as a source of α-Amylase and α-Glucosidase inhibitors.

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***Corresponding author Email address*: pureheart.bm@gmail.com (Basant M. Khader)**

Introduction

Diabetes mellitus (DM) is a general term for heterogeneous metabolic disorders, the main manifestation of which is chronic hyperglycemia. The cause is impaired insulin secretion insulin action, or both (Kerner & Brückel 2014). It is a common disease that has caused serious public concern, and it has emerged as one of the biggest new threats to public health (Guariguata et al.2014). The chronic complications of diabetes mellitus affect many organ systems and are responsible for most of the morbidity and mortality (Tripathi & Srivastava 2006). It can lead to various complications such as diabetic nephropathy, diabetic cardiovascular complications, neuropathy, and eye and liver complications (Meng et al. 2019). It also can confuse the body's immune system. Several immune alterations have been reported in diabetes, with major impairment of cell-mediated immunity and alterations of polymorphonuclear cells, monocytes, and lymphocytes (Calvet & Yoshikawa 2001). Severe macrovascular (cardiovascular disease) and microvascular complications (such as diabetic kidney disease, diabetic retinopathy, and neuropathy) lead to increased mortality, blindness, and renal failure in people with diabetes and overall result in a significant deterioration in the quality of life (Cole. 2020).

The IDF Diabetes Atlas tenth version reviews an endured worldwide growth in diabetes prevalence, confirming diabetes as a significant global challenge to the health and wellness of individuals, households, and societies .537 million adults (20-79 years) are living with diabetes This represents one out of every ten people. This number is expected to further increase to 643 million by 2030 and 783 million by 2045. More than three out of every four adults with diabetes Live in low-income and middle-income countries. In 2021 Diabetes was responsible for 6.7 million deaths at a rate of one death every five seconds. Egypt is one of the 21 countries and territories of the International Diabetes Federation (IDF) Middle East and North Africa (MENA) region. IDF reported that 463 million people have diabetes in the world and 55 million people in the MENA Region; by 2045 this will rise to 108 million. In Egypt, the total adult population is about 58,091,500, and prevalence of diabetes in adults is 15.2% and the total number of cases of diabetes in adults is 8,850,400.

Adjusted for inflation, the economic cost of diabetes increased by 26% from 2012 to 2017 due to rising diabetes prevalence and higher costs per person with diabetes (American Diabetes Association 2018). The economic burden of type 1 and type 2 diabetes in Egypt was calculated using the exchange rate EGP 1 = USD 0.13976 to the equivalent of (25.2 billion EGP) (3.5 billion USD). Direct medical costs were calculated at (EGP 22.3 billion), with DM complications accounting for the highest proportion (65%) (EGP 14.4 billion) (Assaad-Khalil et al. 2017).

Diabetes-like clinical symptoms were described by the ancient Egyptians 3000 years ago. Araetus of Cappadocia was the first to coin the term diabetes (81-133 AD). Later, after rediscovering the sweetness of the urine and blood of patients, he added the word mellitus (the sweetness of honey) in 1675 by Thomas Willis (England) (first noticed by the ancient Indians). It wasn't until 1776 that Dobson (England) first confirmed that excess sugar in the urine and blood was the cause of the sweetness (Ahmed. 2002).

There are several categories of DM, including type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and secondary causes such as endocrine disorders and steroid use. The main subtypes of DM are type 1 diabetes (insulin-dependent diabetes) and type 2 diabetes (no insulin-dependent diabetes), Each has different pathophysiology, symptoms, and treatments, but both can cause hyperglycemia (Sapra & Bhandari 2022). Type 1 diabetes is generally thought to result from the irreversible loss of insulin-producing beta cells. (Meier et al.2005). type 1 diabetes mainly affects patients in children and adolescents it accounts for 5-10% of all diabetes cases worldwide. People with type 2 diabetes cannot produce enough insulin and metabolize it effectively. With this type of diabetes, impossible increase in insulin secretion Encounter by pancreatic β-cells Abnormalities in their function (Halban et al.2014). This form of the disorder is more common in the elderly and accounts for 90-95% of all diabetes cases (Guariguata et al. 2014). Type 2 diabetes is becoming more common, largely due to sedentary lifestyles and rising obesity (Tuomilehto et al.2001). Despite the crucial etiologic role of lifestyle and environmental factors, it has for years been recognized that genetic factors are important for the development of type 2 diabetes (Grarup et al. 2010).

Insulin resistance in target tissues (liver, muscle, adipose tissue, myocardium) is a common symptom of type 2 diabetes, particularly in obese people. As a result, both excess and insufficient glucose is produced. Additionally, increased fatty acid transport to the liver encourages their oxidation, which helps to boost gluconeogenesis, but an absolute excess of lipoproteins encourages hepatosteatosis (Groop & Ferrannini 1993).

Hyperglycemia

Any increase in blood sugar is the result of more glucose entering the body than leaving through the

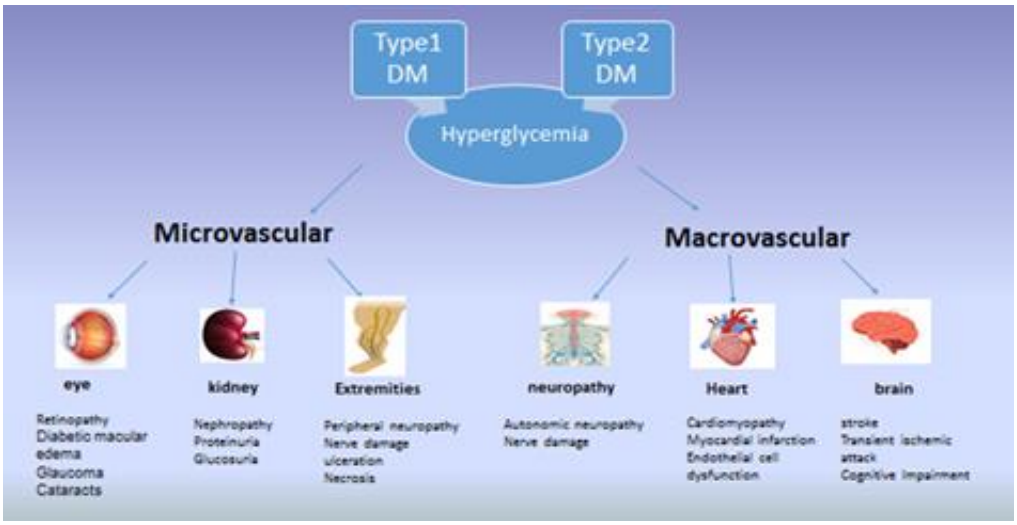

Fig 1. Microvascular and macrovascular complications of diabetes mellitus.

plasma compartment. Hyperglycemia is closely correlated with increased hepatic glucose synthesis when fasting. Further glucose excursions occur after meals because of inadequate insulin stimulation of glucose elimination in target tissues and insufficient inhibition of this glucose output (Inzucchi et al. 2012).

Postprandial hyperglycemia refers to postprandial plasma glucose concentration and is determined by many factors, including meal timing, amount and composition, meal carbohydrate content and composition, insulin, and glucagon secretion, etc. In diabetes, Postprandial hyperglycemia is characterized by hyperglycemic spikes that induce endothelial dysfunction, inflammatory responses, and oxidative stress, which can lead to the progression of atherosclerosis and the development of cardiovascular events. Therefore, postprandial hyperglycemia is one of the most important pathophysiological disorders leading to vascular disease. (Node & Inoue 2009). With rising hyperglycemia concentrations, the chance of acquiring diabetic complications rises. In, type 2 patients, lowering hyperglycemia lowers the risk of complications (Stratton et al. 2000).

The postprandial increase in blood glucose levels is primarily the result of carbohydrate hydrolysis, a process catalyzed by the enzymes α-glucosidase and α-amylase (Watanabe et al. 1997). An α-amylase called petyaline is produced by the salivary glands where it acts as a monomer and mediates the hydrolysis of α-1,4-glucosidic bonds of oligosaccharides. α-Glucosidase located in the brush border of the small intestine hydrolyzes terminal non-reducing (1→4)-linked α-glucose residues to release a single α-glucose molecule After that, it is absorbed into the blood from the small intestine, and the remaining oligosaccharides are hydrolyzed by pancreatic amylase which secreted from the pancreas into the small intestine (Mwakalukwa et al. 2020).

Synthetic inhibitors of α-amylase and α-glucosidase enzymes

The most difficult goal in treating diabetes mellitus patients is to bring blood sugar levels as close to normal as possible. To date, 6 classes of oral antihyperglycemic drugs are available: biguanides (metformin), sulphonylurea (eg, tolbutamide, chlorpropamide), glinidines (eg, repaglinide, nateglinide), thiazolidinediones (e.g., pioglitazone), dipeptidyl peptidase IV inhibitors (e.g., sitagliptin, saxagliptin) and alpha-glucosidase inhibitors (AGIs; eg, acarbose) (Nathan et al. 2007).

α-amylase and α-glucosidase inhibitors are antidiabetic drugs that act by competitively inhibiting α-amylase and α-glucosidase. These inhibitors slow the digestion of carbohydrates and thus postprandial glucose absorption, leading to attenuation of postprandial plasma glucose and insulin levels and diabetic patients (Priebe et al. 2018). α -glucosidase inhibitors are advised by many national and international guidelines as a first-line option to metformin or in combination with sulfonylureas, metformin, other more recent oral hypoglycemic medications, or insulin (Joshi et al. 2015).

The synthetic drugs of this kind that have been studied the maximum notably are acarbose, miglitol, and Voglibose of which voglibose is the newest. The mechanisms of action of these different inhibitors are similar though not identical. (Ismail & Deshmukh 2012).

Acarbose is a complicated oligosaccharide (tetrasaccharide derivative) that acts as a competitive, reversible inhibitor of alpha-glucosidase and pancreatic alpha-amylase with antihyperglycemic activity (Joshi et al. 2015). Acarbose is structurally like natural oligosaccharides but has a 10 to 10-fold higher affinity for α-glucosidase. This competitively inhibits these enzyme complexes and reduces the availability of oligosaccharides from food starch. (Rosak & Mertes 2012).

Miglitol, on the other hand, is a small molecule (iminosugar), carefully associated with glucose inside the pyranose shape and is properly absorbed with a100% systemic bioavailability (Ramsch et al.1985). Miglitol has low inhibitory activity against lactase. Neither acarbose nor voglibose shows inhibitory activity against lactase (Dabhi et al. 2013).

Voglibose is an N-substituted derivative of valiolamine, a reversible inhibitor of membrane-bound intestines α glycosidase hydrolize. Voglibose delays the absorption as well as digestion of dietary polysaccharides (Dabhi et al. 2013). Being a new potent glucosidase inhibitor, it has shown potent anti-obesity and anti-diabetic activity (Chen et al. 2006).

Because these inhibitors have significant side effects such as diarrhea, abdominal discomfort, and gastrointestinal disturbances, new molecules with fewer side effects are needed (Singh & Kaur 2016; Playford et al. 2013).

Endophytic fungi

Endophytic fungi are a group of microorganisms that inhabit plant tissues throughout all or part of their life cycle without causing adverse effects or diseases and they can be fungi, bacteria, and actinomycetes. The term endophyte came from two Greek words: "endon" meaning inside and "phyton" meaning plant. The term “endophyte” was first proposed by de Bary in 1866 as “any organism that grows within plant tissues are termed as endophytes,”. Since its first description in Darnell (*Lolium temulentum*) (Freeman. 1904), endophytes have been isolated from various organs of various plant species, bryophytes, lycophytes, ferns, and tropical spermatozoa. have been separated. To the Arctic, from wilderness to agroecosystems (Arnold. 2007). over 100 years of research suggests that most, if not all, plants in natural ecosystems are symbiotic with fungal endophytes (Petrini. 1986). plants and fungal endophytes interacted since approximately 400 million years ago, fossilized fungal hyphae and spores from the Wisconsin Ordovician period (about 460 million years old) closely resemble modern arbuscular mycorrhizal fungi (Glomales, Zygomycetes), these fungi may have played a vital role in facilitating land colonization of plants (Krings et al. 2007).

Fungal endophytes constitute a major part of unexplored and underrated fungal diversity. Remarkably, of the approximately 300,000 species of plants that exist on Earth, all have one or more endophytes. Few of these plants have been thoroughly studied from an endophytic point of view. As a result, the opportunities to discover new and interesting endophytic microorganisms among myriad plants in a wide variety of environments and ecosystems are great (Strobel & Daisy 2003).

Exciting possibilities exist for using endophytic fungi to produce copious quantities of known and novel biologically active secondary metabolites (Kusari et al.2012, Yan et al. 2011). The number of secondary metabolites produced by fungal endophytes is greater than any other class of endophytic microorganisms. This may be the result of frequent isolation of fungal endophytes from plants (Zhang et al.2006). Fungal endophytes provide a rich and diverse source of bioactive molecules being continuously explored for food, health, and environmental applications.

Fungal endophytes have been classified according to evolutionary relatedness, taxonomy, host plant range, and ecological function into two groups, the clavicipitceous (C) and the non-clavicipitaceous (NC) (Rodriguez et al. 2009).

Endophytes are dormant in some parts of plants, and their growth and biochemistry are influenced by plant products (Stone et al. 2000). The interactions between endophytic fungi and host plants are deciphered as a balance under environmental, physiological, and genetic control, resulting in fitness benefits for both partners (Kogel et al. 2006). The concept of balanced antagonism implies that endophytes proactively prevent the activation of host defenses Inactivated by host toxic metabolites. This allows endophytes to grow invisibly within the host (Silva et al. 2022). Further research at the molecular level in this area is needed to better understand host-endophyte interactions (Tan & Zou 2001).

The major factors controlling endophytic colonization within a plant include plant genotype, plant growth stage, plant physiological state, plant tissue type, and soil environmental conditions. Cultivation methods, sampling times, surface sterility, selective media and culture conditions, and various agricultural practices (Gaiero et al.2013). Endophytes can contribute to the host plant by producing substantial amounts of substances that provide protection and ultimately survival value to the plant (Strobel et al.2004). and some of these compounds are useful in new drug discovery (Guo et al .2008).

During the long co-evolution of endophytes and their host plants, endophytes have adapted to specific

microenvironments through genetic variation, including integrating portions of plant DNA into their genomes (Germaine. 2004). Their co-evolution means that endophytes produce compounds that are the same or similar to those derived from plants (Kaul et al.2012).

Endophytic fungi as a source of natural bioactive products

Secondary metabolites are natural products that play no direct role in the uptake, development, and reproduction of organisms. In microbes (such as endophytes), they are specific to specific ecological niches, mainly for specific phenotypic functions (crosstalk with related organisms, chemical warfare/defense, etc.) It is biosynthesized under biotic or abiotic selection pressure (Kusari et al. 2014). They are a continuous source of new bioactive substances A metabolite with widespread effects on modern human medicine. About 68% of antimicrobial compounds and 34% of products used to treat cancer are both Natural products and their derivatives (Newman & Cragg 2007).

Endophytes are a rich source of novel organic compounds with interesting biological and chemical activities with elevated levels of biodiversity (Tan & Zou 2001). Natural products from fungal endophytes have a wide range of biological activities and include several alkaloids, steroids, terpenoids, isocoumarins, quinones, phenylpropanoids and lignans, phenolic and phenolic acids, aliphatic metabolites, lactones, etc. (Schulz et al.2002). Bioprospecting of endophytes to search for novel metabolites has attracted a great deal of attention worldwide (Gouda et al. 2016). certain endophytes biosynthesize some of the 'phytochemicals' originally associated with the host plant (Stierle et al. 1993). Extraction from plant sources has several drawbacks, such as dependence on seasonal, climatic, and political conditions, as well as potential ecological problems associated with extraction (Shukla et al. 2014). As a result, direct production of these substances from plant tissue may be substituted since many endangered plant species have been reported to be indiscriminately used in search of therapeutic methods (Chen et al.2016). Due to the short generation time, fast growth rate, high biomass production, and good handling in bioreactors of microorganisms, endophytes are suitable to produce functional substances in various fields such as medicine, agriculture, and industry. In contrast to slow-growing endangered host plants (Guo et al. 2008; Ludwig-Müller 2015).

Taxol, which was the first anticancer drug discovered, was found in small quantities in *Taxus sp*., slow-growing trees found in the Pacific regions. Taxol has become one of the best-selling anticancer drugs worldwide. *Taxomyces andreanae*, a fungal endophyte, were isolated from the phloem (inside the bark) of the Pacific yew *Taxus brevifolia*. This fungus is a filamentous fungus that produces taxol and related compounds when grown in semi-synthetic liquid media (Stierle et al. 1993). In addition to the clinically recognized antineoplastic agent Taxol, studies of endophytes have identified potential agents including antimicrobials, antioxidants, anticancer, antivirals, antidiabetics, anti-alzheimer's agents, anti-rheumatoid, and immuno-suppressants. is produced (Salem & Abdel-Azeem 2014; Abdel-Azeem et al. 2016; Abo Nahas et al. 2023). These discoveries offer hope for tackling terminal diseases, drug resistance, and other human health challenges (Shukla et al. 2014).

Endophytic fungi, particularly those from higher plants, have become a rich source of bioactive and novel chemicals with fascinating biological roles and a high level of variety (Abdel-Azeem et al. 2018; Attia et al. 2020; Balbool & Abdel-Azeem 2020; Balbool et al. 2020; Romeiro dos Santos et al. 2021; Moubasher et al. 2022; Mohamed et al. 2023).

Endophytic fungi from medicinal plants

To isolate novel endophytic microorganisms and create the best methods to produce novel bioactive substances, it is important to understand the methods and rationale used. Given the sheer number of plant species in the world, creative and imaginative strategies must be employed to rapidly narrow down the search for bioactive endophytes (Strobel & Daisy 2003).

Selection of plants for endophytic isolation is based on four selection strategies according to Abdel-Azeem et al. (2019) as follows:

1- Plants growing in areas of high biodiversity may also harbor high biodiversity endophytes.
2- Plants that grow in special habitats, especially degraded ecological environments, have special viability.
3- A plant that is somewhere utilized as a traditional medicine for human use (ethnobotanically important plant).
4- Certain ancient land-dwelling plants are more likely than others to possess endophytes with active natural products (Endemic plants).

When comparing endophytic hosts, medicinal plants are the most frequently used (35%), followed by crops (29%), special environment plants (18%), and other plants (18%) (Yu et al. 2010).

Medicinal plants have existed since time immemorial Used as raw material for medicine. Almost all cultures of the world know the therapeutic properties of local plants (Kaul et al. 2012) In recent years, herbal medicine has

received increasing attention and Popularity in the current medical and commercial field. Despite the long history, of the identification of the use of herbal medicines in folk medicine the use of active herbal ingredients may lead to the discovery of new perspectives Therapeutic applications, and the production of natural medicines (Amer & Mohammad 2022). Traditional medicine used since ancient times for the treatment of human diseases in Egypt (Abdel-Azim 2011) The medicinal use of herbal preparations in Egyptian culture dates to 1900 BC. Documented. In medical manuscripts on papyrus. The "Egyptian Pharmacopoeia" contains remedies of plant, mineral, and animal origin, containing over 700 medicines for the treatment or alleviation of over 200 different ailments (Abu-Elsaoud 2010) A considerable number of Egyptian herbs are known to be used in folk medicine. Many Egyptian medicinal plants are used in the treatment of a wide variety of diseases e.g., diabetes. (Boulos 1983, Abdel Wahab et al. 1987).

Medicinal plants are a valuable source of herbal products worldwide. Medicinal plants contain various chemicals with important therapeutic properties that can be used to treat human diseases. Up to 80% of people in developing countries combined rely on herbal medicine for basic medical care, and over 25% of prescribed drugs are developed Country comes from wild plant species (Hamilton 2004). According to WHO, 65% to 80% of the population in developing countries currently uses medicinal plants as medicines.

Plants used in traditional medicine are a rich source in the search for new bioactive endophytic fungal strains. The endophytic diversity of plants of medicinal importance has received increasing interest in recent years as it plays a vital role in the discovery of natural products. Screening bioactive compounds from fungal endophytes isolated from medicinal plants is considered a promising avenue for discovering highly abundant and diverse new molecules that are used in the treatment of many diseases. They are therefore the basis for new drugs discovered.

Techniques of Bioprospecting Endophytes and their bioactive product

After a plant is chosen for study, it's far identified, and its place is plotted with the usage of a global positioning device. The first step to observe endophytic fungi is the gathering of plant material. The samples ought to be in a sterile plastic box or bag, transferred to a groovy field at a managed temperature till isolation strategies can start, and ideally processed within 24 hours after sampling.

A typical surface sterilization protocol involves washing the plant material under running water, and chemically sterilizing it using one or more chemicals such as ethanol, sodium hypochlorite, or mercuric chloride, followed by thorough rinsing with water. rinsing and finally inoculating the sterile explants into an appropriate medium. An effective sterilization protocol removes all epiphytic bacteria with little or negligible phytotoxicity. (Abdel-Azeem & Salem 2012, Sahu et al. 2022).

Several media protocols are available for acquiring endophytes. Depending on research objectives and habitat characteristics, commonly used media can be supplemented with nutrients or replaced with specific media to better achieve research objectives (dos Reis 2022).

Morphological and molecular identification of isolated endophytes is based on using relevant identification keys and confirmatory sequencing by 18S rRNA gene or ITS rDNA sequence (ITS1 or ITS2 internal transcribed spacer) (Wijekoon 2021).

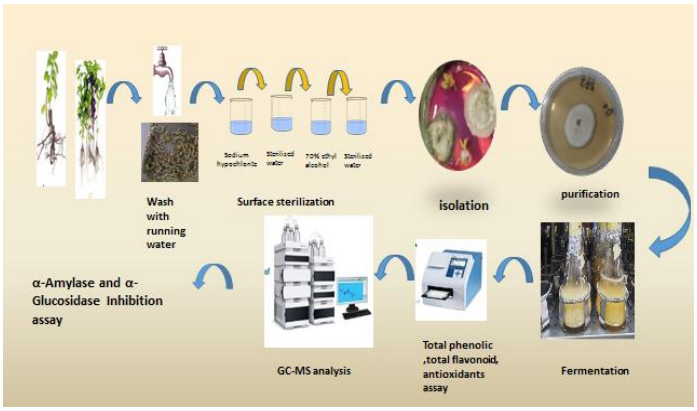

Fig 2. Bioprospecting endophytes and their bioactive product e.g. antidiabetic inhibitor.

Endophytic fungi as a potential source of antidiabetic agents

Nature has provided natural resources with a rich, vast, and highly diverse chemical database that can be searched for potential therapeutic agents through bioactivity-directed screening. Many plants have been reported to have antidiabetic effects by inhibiting the enzymes α-amylase and α-glucosidase (Nair 2013). However, microbial sources of bioactive compounds are easier and more economical to produce (Zhang et al. 2006; Strobel et al. 2004; Schulz et al. 2002). Although endophytes live within plants, they do not harm the host plant and are relatively understudied as a major source of bioactive metabolites such as antidiabetic drugs (Bilal et al.2018; Artanti et al. 2012; Pavithra et al.2014; Ye et al.2021). The ability of endophytic fungi to co-produce bioactive compounds with their host plants provides an

opportunity to obtain natural, inexpensive, and environmentally friendly precursors to antidiabetic drugs (Dompeipen 2011).

Over the past decade, scientists have tried to take advantage of the fact that the endophytic fungi isolated from antidiabetic medicinal plants can produce the same bioactive compound that the plant produces in their attempt to extract and find an effective treatment to inhibit alpha-amylase and alpha-glucosidase enzymes. Endophytic fungi are a potential source of novel antidiabetic drugs.

Grifola frondosa has been used as a remedy for type 2 diabetes, and its extracts can impact hyperglycemia and hyperinsulinemia (Poucheret 2006).

Colletotrichum sp. TSC13 endophytic fungi isolated from *Taxus sumatrana* has been described as a source of three unsaturated fatty acid methyl esters, oleic acid, linoleic acid, and linolenic acid methyl esters and two saturated fatty acid methyl esters, palmitic acid and stearic acid methyl esters that exhibits inhibitory activity against α-glucosidase Unsaturated fatty acids showed higher activity than the saturated fatty acids. So, conclusion was reached that the alpha-glucosidase inhibitor compounds in *Colletotrichum sp*. TSC13 were unsaturated fatty acids. (Artanti et al., 2012).

Two naphthoquinones were isolated by chemical analysis of the culture filtrate of the endophyte *Dendryphion nanum* (Nees) S. Hughes isolated from the leaves of *Ficus religiosa* collected from Goregaon, Mumbai. Compound 1 induced glucose uptake in the rat skeleton muscle in the presence of insulin with an EC50 of 0.80±0.090uM. rosiglitazone, known glucose uptake activator (EC50 = 3.0 ± 0.040 μM) Assay standard. (Mishra et al. 2013).

Bioassay fractionation of bioactive organic extracts obtained from solid-media cultures of MEXU 27095, an endophytic fungus isolated from the Mexican medicinal plant *Hintonia latiflora (Rupiaceae)*, revealed thilavins A, J, and three tridepsides identified as K were isolated. The compounds inhibited Saccharomyces cerevisiae α-glucosidase (αGHY) in a concentration-dependent manner with IC50 values of 23.8, 15.8, and 22.1 μM, respectively. Their inhibitory interest changed better than that of acarbose (IC50=545 μM) used as a positive control (Rivera-Chávez et al. 2013).

Twenty-two endophytes were isolated from the antidiabetic plants *Momordica charantia* and *Trigonella foenum-graceum*. Ethyl acetate extracts of all endophytic fungal isolates were tested for inhibition potential of aldose reductase and carbohydrate-metabolizing enzymes. extracts from nine endophytic isolates were positive for α-amylase and α-glucosidase inhibitors. Crude extracts of fungal isolates PTFL005 and PTFL006 showed promising inhibitory activity against α-amylase with IC 50 values of 15.48 and 13.48 μg/ml, respectively. In contrast, control acarbose had an IC 50 value of 22.38 μg/ml against α-amylase under similar experimental conditions. Extracts of fungal isolates PTFL006 and PTFL011 showed to have potent α-glucosidase inhibitors with IC 50s of 17.37 and 10.71 μg/mL, close to standard acarbose (6.53 μg/mL). (Pavithra et al.2014).

The endophytic fungus *A. awamori*, isolated from the stems and leaves of *A. nilotica* plants, can produce peptides with α-glycosidase and α-amylase inhibitory activity. UHPLC amino acid analysis showed the presence of serine, threonine, tyrosine, and valine amino acids in the peptide The purified inhibitor exhibited a mixed type of inhibition against alpha-amylase and alpha-glucosidase with IC50 values of 3·75 and 5·625 μg ml^{-1} respectively. (Singh & Kaur 2016).

The ability of *Paecilomyces formos* LHL10, an endophytic fungus isolated from the roots of cucumber plants, was tested to inhibit enzymes. The structures were elucidated by spectroscopic analysis and comparison with literature data, confirming that purified compounds are known ester terpenoids (1) and known cyclic peptides (2). As a result, it was shown that compound 1 and compound 2 exhibited a significant inhibitory rate against α-glucosidase in a dose-dependent manner. Acarbose (100 μg/ml) was used as standard. Compounds 1 and 2 exhibited statistically significant activity against α-glucosidase, achieving approximately 75.23% and 67.21% inhibition with IC50 values of 61.80±5.7 and 75.68±62 μg/mL, respectively (Bilal et al. 2018).

A pyridone alkaloid with an unusual pyrano [3,2-c] pyridine backbone, asperpyridone A (1), has been isolated from solid cultures of the endophyte *Aspergillus*. isolated. TJ23. Related to the leaves of *Hypericum perforatum*. In vitro bioassays showed that asperpyridone A (1) may act as a potential hypoglycemic agent, showing pronounced glucose uptake effects in HepG2 cells of the liver under normal and insulin-resistant conditions, It showed higher potency than metformin (Qiao et al. 2019).

Three novel fumiquinazoline alkaloids and 12 known fumiquinazoline alkaloids have been isolated and characterized from the marine fungus *Scedosporium apiospermum* F41-1. The antidiabetic potential was tested by measuring the antidiabetic activity of the compounds by determining their triglyceride-promoting activity using 3T3-L1 adipocytes. New compounds, scequinadoline J (14), D (9), and E (10) were found to promote triglyceride accumulation in 3T3-L1 cells. Scequinadoline D (9) demonstrated the most potent activity, with an EC50 value of 0.27 ± 0.03 μM (Li et al.2020).

Three α-glucosidase inhibitory xanthones (5, 7, and 11), of which 5 are described for the first time isolated from the endophytic fungus *Penicillium canescens* from the fruit of *Juniperus polycarpos* which has been used as antidiabetic traditional medicine. The three xanthones 5, 7, and 11 exhibited inhibitory activity against α-glucosidase with IC50 values of 38.80 ± 1.01 μM, 32.32 ± 1.01 μM, and 75.20 ± 1.02 μM, respectively (Malik et al. 2020).

Six new diketopiperazine alkaloids aspergiamides from 1 to 6, together with ten known alkaloids from 7 to 16, were isolated from the endophytic fungus *Aspergillus* sp. 16-5c which was isolated from the leaves of *S. apetala*, a mangrove plant that was collected from Hainan Island, China. These compounds were evaluated the antidiabetic potential by screening the enzyme inhibition of α-glucosidase. The bioassay results disclosed compounds 1 and 9 showed potent α-glucosidase inhibitory with IC_{50} values of 18.2 and 7.6 μM, respectively; compounds 3, 10, 11, and 15 showed moderate α-glucosidase inhibition with IC_{50} values ranging from 40.7 to 83.9 μM (Ye et al. 2021).

Conclusion

This is due to the steady increase in the number of people with diabetes in recent years and the impact diabetes has on patients' health and personal financial burden. There is growing research interest in finding new effective and safe drugs from natural resources. endophytic fungi have proven to be a rich and safe source of bioactive compounds that can be used in medicines such as anti-diabetic drugs. The study of endophytic fungi is an exciting new avenue for biotechnology, with the potential to discover new ways to commercially exploit fungal species to detect bioactive compounds that can be used to meet the demands of the pharmaceutical industry.

Conflict of interest

The authors have no conflicts of interest to declare.

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