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Endophytic fungi as a source of antidiabetic metabolites: A review

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Abstract:
Diabetes is one of the most fatal non-communicable illnesses and prevalent among the adult population globally. Endophytic fungi, which are fungi living in the host plant, have been recently recognized as a potential source of secondary metabolite compounds. Interest has expanded in recent years in fungal endophytes as a source of antidiabetic metabolites. Endophytic fungi constitute a rich source of bioactive natural products and have the potential to contribute significantly to the identification of new antidiabetic metabolites. Recent progress in the isolating of active compounds with antidiabetic activities from endophytes has identified a number of novel compounds. Furthermore, the biotechnological applications of antidiabetic metabolites have also been explored. In conclusion, fungal endophytes offer a potential source of antidiabetic metabolites and further research is needed to validate the efficacy and safety of novel antidiabetic compounds derived from endophytic fungi.

Keywords: Diabetes, Antidiabetic, Compounds, Endophyte, Fungi.

1. Introduction

Diabetes mellitus (DM) has become an increasing health problem globally because it affects individuals of all ages and raises the chances of other ailments like cardiovascular disorders and renal damage [1]. The World Health Organization (WHO) reports that non-communicable illnesses account for almost 74% of deaths including diabetes, cancer, cardiovascular diseases and chronic respiratory diseases [2, 3]. DM is a significant global health illness characterized by increased blood glucose concentrations, that results in problems such as hypertension, retinopathy, neuropathy as well as diabetic foot ulcers [4]. Plants serve as the natural inhabitants of microbes. A symbiotic relationship exists between them so as to achieve their requirements. The word "endophyte" was first presented by a scientist called De Bary in the year 1866 and means any organism present in the tissue of plant which is distinct from those living (epiphytes) on plant surfaces. Many scientists define endophytes as mutualists of microbes, that colonize aerial portions of living plant tissues with no symptoms of the disease [5]. Endophytic microorganisms and their derivative active metabolites are vital natural sources of promising therapies. Great attention was devoted to the therapeutic prospective of endophytic fungi and their metabolites as biotherapeutics [6]. Several significant secondary metabolites including anti-diabetic, anti-fungal, anti-cancer and immunosuppressant compounds are derived from endophytes [7].

It is expected that in spite of the multi-disciplinary research addressed in the investigation of fungal endophyte and its different active metabolites, the area is yet at its infancy, with small success in synthesizing metabolites for commercial motive. Hence, the application via biotechnological approach of endophytic fungi in deriving of relevant natural metabolites from plant became essential [8]. This review indicated that fungal endophytes can be utilized to produce an alternative bioactive metabolite that can be used in managing diabetic conditions. It also highlighted the manner in which diabetes affect million individuals globally, hence, the search for antidiabetic from natural source is of paramount importance.

2. Diabetes mellitus

Diabetes mellitus is a metabolic condition that causes increase in glucose level (hyperglycemia), a disorder that may involve defective secretion of insulin and/or action [9]. The number of cases of diabetes has gone up globally from two hundred and eighty five (285) million adults in the year 2009 to three hundred and eighty two (382) million in 2013, with an expected four hundred and seventy one (471) million by the year 2030 [10-12]. Diabetes is a chronic disease that affects nearly 537 million adults globally, making it one of the key chronic diseases among non-communicable diseases. It has been estimated by the WHO and International Diabetes Federation that the worldwide diabetes prevalence would go beyond seven hundred and three (783) million people by the year 2045 [3, 13]. In Nigeria, some experts have stated that diabetes affects roughly 11 million Nigerians [14, 15].

DM is linked to insulin resistance and the failure of β-cells of pancreas to synthesize insulin, leading to increase in glucose levels. Furthermore, increase in glucose levels is linked with polyuria, polydipsia, , ketoacidosis, weight loss and other deadly health conditions [16]. Two different categories of diabetes exist, type 1 DM characterized by lack of insulin synthesis and type 2 DM characterized by resistance to insulin action [17]. Type 2 DM is one of the most common and significant metabolic disorders in the world [18, 19].

In diabetic condition, the postprandial hyperglycemia (PPHG) phase is characterized by a quick and large increase in blood glucose levels, there has been a lot of attention on the potential of these postprandial "hyperglycemic spikes" to the pathophysiology of late diabetes complications [20]. Post prandial phase is caused because of the action of two enteric enzymes namely α-amylase and α-glucosidase. Thus, inhibition of both enzymes slows the carbohydrates digestion and the absorption of glucose [21]. The type 2 DM, a non-insulin dependent DM is the most prevalent, its management is complicated by certain factors associated with the disease and elevated postprandial hyperglycemia is one of the risk factors which is raised by the glucosidases [22]. Glucosidase catalyse the release of α-glucose from the substrate's non-reducing end. Inhibition of this enzyme slows the rise of glycemia following a meal containing carbohydrates [23].

The inhibitors of α -glucosidase play a main role in management of postprandial hyperglycemia in diabetic patients. The decrease in hydrolysis of starch is caused by inhibition of α -glucosidase enzyme activity, which has valuable effects on the control glycemic index in diabetic patients [24]. Glucosidase inhibitors like inhibitors of α-amylase play a key role in treatment of PPHG in diabetic patients. These α-amylase inhibitors exhibit inhibitory activity on the α-amylase enzyme resulting in a decrease in starch hydrolysis that has useful effects on glycemic index control in patients with diabetes [25]. Postprandial hyperglycemia is lowered by α-glucosidase inhibitors such as acarbose, miglitol, and voglibose mainly by interfering with the enzymes that digest carbohydrate and delaying glucose absorption [26]. Though inhibitors of α-glucosidase have been used clinically since 1990, but only three are commercially available including; miglitol, acarbose and voglibose. They are commonly connected with side effects on gastrointestinal tract, mostly diarrhea and flatulence [27]. Miglitol and acarbose are regularly reported to yield other intestinal instabilities [28]. Therefore, herbal therapy can be an effective approach to counter the side effects of synthetic drugs. A variety of medicinal plants have been used traditionally for the management of diabetic condition [29]. Alpha-glucosidase inhibitors have been found in nature to be a encouraging source of compounds, some of which have been isolated from plants with medicinal values [30-32]. In recent years, there have been significant efforts to discover effective α -glucosidases inhibitors of natural origin [33].

3. Endophytic Fungi

Endophyte was once used to describe any organisms that occur and colonize plant internal tissues without producing obvious impairment to the host [34]. Endophytic fungi synthesizea range of metabolite compounds of diverse chemical classes, comprising alkaloids, flavonoids, phenolic, steroids and terpenoids [35]. Because of long endophytic host-parasitic relationship may produce even secondary metabolites as plants. They are a significant source of metabolites such as antidiabetic, antibacterial and antifungus activity [36]. Exploiting fungal endophytes from plants is eco-friendly, as only a small part of the plant like flower, leaf, bark and fruit is utilised for the study. When the culture are well-maintained they are renewable and have many benefits, like being able to be preserved in perpetuity and modified genetically to improve their usefulness [37]. Exporting endophytic microflora is a footstep towards preserving plants of medicinal important from extinction. It boosts to harvest of metabolites of medical significance from endophytic microbes as an alternative of the host plant species [38, 39]. It has been described that endophytes have the capability to synthesize similar or the same chemical metabolites as those originating from their host plants, as such endophytic microbes serve as the potential substitutes to plants in the quest for the active biological compounds [40]. Nearly every plant species, about 400,000 have one or additional endophytes [5]. However, only insufficient plants have been expansively studied for their endophytic biodiversity as well as their capacity to synthesize the main active secondary metabolite compounds [41]. Endophytic fungi have a higher number of bioactive compounds, this is as a results of their diversity and endophytes are reasonably fast-growing on artificial media [42, 43].

4. Beneficial role of endophytic fungi to the host plant

The association between plants and endophytes has existed for over 400 million years [44]. Endophyte interaction is described as a balanced antagonism, triggering mechanisms of virulence for colonisation and activation of host defenses is necessary when the plant is recognized as a host. When the interaction is at equilibrium the fungal microbes lives of nutrients derived from the host and, in interchange, offers benefits comprising tolerance to abiotic and biotic stresses [45]. Endophyte-related plants are recognized to establish metabolites that cause pathogen resistance. Moreover, secondary metabolites such as lytic enzymes and antibiotics produced by these endophytes provide defense against a range of pathogenic agents [46]. Endophytes that are linked to medicinal plants provide a bioactive metabolite source that is environmentally friendly. In terms of their biosynthetic pathways, they can be the primary producers of certain active components, or at least can offer the host plant with additional chemical defense so as to deal with the surrounding stress conditions [47]. Fungal endophytes were reported to provide defense to their hosts against pathogens, insects, pests and even several herbivorous [48]. They also have some exo-enzymes that help to improve colonise their hosts and are capable of growing well in the apoplastic washing fluid of their host. As a result, endophytic fungi employ those biotopes of his and directly or indirectly rise the level of secondary active metabolites [49]. Moreover, phytohormones produced by fungal endophytes can encourage the growth of their host plant [50].

5. Endophytic fungi as the source of antidiebetic metabolites

The metabolic system of fungi is distinct and enables them to synthesize a diversity of natural products that have an impressive chemical diversity, which is a unique characteristic of fungi. They are therefore seen as one of the richest sources of naturally occurring products in living organisms [16]. They are an important source of secondary metabolite compounds like alkaloids, tannins and phenolics compounds [51, 52]. Endophytic fungi provide antidiabetic agents [53-55].

In a study of Kantari *et al.,* [57], endophytic fungi *Nigrospora sphaerica* was isolated from *Bauhinia purpurea* L. and screened for antidiabetic actions. Ethyl acetate extract of *N. sphaerica* exhibited high level of inhibitory activity of alpha-glucosidase with an IC_{50} value of 0.020 ± 0.001 mg ml^{-1}. The value (0.494 ± 0.009 mg ml^{-1}) was significantly higher than the standard drug acarbose [56]. Another study was carried out to evaluate the fungal endophytes from different plants namely; *Azadirachta indica, Mangifera indica and Syzygium cumini L.* The results revealed that an aqueous extract of fungal isolated from *S. cumini L* at 200µg/ml displayed significant amylase inhibition of 62% [57]. The Table 1 below shows the antidiabetic activities of some endophyte derived-metabolites from some plants.

Table 1: Antidiabetic potential of some endophyte derived-metabolites from some plants

Endophytic fungi	Plant source	Metabolites/extracts	Antidiabetic activity of metabolites/extracts	References
Nigrospora oryzae	*Combretum dolichopetalum*	Three metabolites were isolated including (1) (S)-(+)-2-cis-4-trans-abscisic acid (2) 7'-hydroxy-abscisic acid (3) 4-des-hydroxyl altersolanol A	The extract and the metabolites 1 to 3 significantly ($p<0.001$) decreased the fasting blood sugar levels of the experimental diabetic mice.	[58]
Curvularia lunata	*Ficus religiosa*	Phytochemical analysis of the fungal extracts shown the presence of alkaloids, flavonoids, phenols, steroids, terpenes and terpenoids	The Ethyl acetate extract of the fungal strain at a concentration of 0.5 mg mL-1 showed an inhibition of 80.4%. Standard α-amylase inhibitor - Acarbose showed an inhibitory activity of 98.8%.	[59]
Alternaria longipes strain	*Avicennia officinalis*	2,4,6-triphenylaniline	The diabetic rats received oral administration. 2,4,6-triphenylaniline (10 mg/kg bw) and the standard drug metformin (10 mg/kg bw) respectively one daily for a period of 48 days. After intervention period, 2,4,6-triphenylaniline showed controlled blood glucose	[60]
Alternaria sp.	*Cynanchum acutum* L. (Apocynaceae), *Lycium schweinfurthii* Dammer (Solanaceae) and *Pancratium maritimum* L. (Amaryllidaceae)	Six phenolic compounds were isolated including; (1) Talaroflavone (2) Alternarienoic acid (3) Altenuene (4) Altenusin (5) Alternariol (6) Alternariol-5-O-methyl ether	An in vitro α-glucosidase inhibitory assay of the compounds isolated as well as the positive control acarbose revealed that compounds 2, 3 and 4 have potent α-glucosidase inhibitory activity with IC_{50} values 7.95 ± 1.2, 40.38 ± 3.7 and 46.14 ± 0.84 µM, respectively	[61]

6. Conclusion

Diabetes is a chronic disorder that affects nearly 537 million adults globally, making it one of the main chronic diseases among non-communicable diseases. The number of cases of diabetes has gone up worldwide. While the type 2 diabetic is the most prevalent disorder globally. Adverse effects of the commercially prepared drugs are major concerns that requires an alternative approach. This review indicated that fungal endophytes can be utilized to produce an alternative bioactive metabolite that can be used in managing diabetic conditions. Considering, the diverse nature of endophytic fungi and the fact that endophytes can be modified genetically, more research needs to be done to isolate various metabolites and to also validate the effectiveness for antidiabetic.

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