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Endophytic Fungi from Medicinal Plants: Unexposed niches for Novel bio active compounds – Review

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ABSTRACT

Endophytic fungi belongs to the group of fungi which Colonizes the plant parts like stem, roots, leaves without causing any tissue damage and symptoms. The biggest advantages of endophytic fungi are their fast renewal, relatively easy cultivation, cost-effectiveness, and environmental safety. Numerous bioactive substances with a wide range of activities have been found in endophytic fungi over the last 20 years. Numerous medically important endophytic fungi are isolated from variety of medicinal plant around the world. Hence, this review aims at presenting the richness in bioactive antimicrobial compounds of the endophytic fungi isolated from different medicinal plants. Importantly, tracing the previous findings would pave the way to forecast the missing link for future work by researchers. This review confers the isolated secondary metabolites from different endophytic fungi identified and reported along with their reported biological activities and structural aspects whenever applicable. This review presents a discussion on some fundamental aspects of phytomedicinal chemical production by endophytic fungi with an overview of several medicinal plants that have received considerable use and attention over the past decade.

Key Words: Medicinal plants, Endophytic fungi, Natural activity, Secondary metabolites, Pharmacological activity

INTRODUCTION

Generally plant harbors diverse groups of microbe's either part of their life cycle or completely as endophytic organisms and these organisms are categorized into different domains. These microorganisms encompass bacteria, fungi, archaea, algae, and protists. They play a crucial role in the plant's microbiome and can thrive within the healthy tissues of the host plant without causing visible signs of disease. They engage in complex physiological relationships with their host plants and other microbes, including endophytes and epiphytic pathogens [1]. Endophytes, serving as vital microbial allies, have a widespread presence in both medicinal and non-medicinal plants [2]. They serve as productive factories for synthesizing bioactive compounds, which play a protective role for the host plants against various threats, including plant pathogens, pests, and nematodes. Additionally, they act as growth promoters and inducers of tolerance to both biotic and abiotic stress (Lee, Kendall, et al., 2021). Furthermore, they function as effective bioremediation agents (Dell' Anno et al., 2021; Nikolopoulou, et al., 2013). The association between host internal tissue and fungal endophytes is extensively connected with adaptations in colonization of the endophyte and extraction of its natural bio- active compounds [3,4,5].The vast body of literature provides in-depth insights into the chemical compositions and organic properties of the active metabolites produced by medicinal plants [6,7]. However, the investigation into active metabolites synthesized by endophytic fungi has been notably limited. These endophytic fungi possess the capacity to produce metabolites that are structurally similar and pharmacologically active, either in conjunction with their host plant or as exclusive producers [8-10].

Globally, the issue of Antimicrobial Resistance (AMR) has become a severe public health concern. The notable reasons behind the rise of drug resistance include the inappropriate use and overuse of chemotherapeutic agents in both healthcare and agricultural settings. Key contributors to antimicrobial resistance involve bacterial mutations, spontaneous genetic alterations, and the horizontal transfer of resistance genes. The situation is exacerbated by the proliferation of resistant strains and the diminishing effectiveness of chemotherapeutic agents. Consequently, there is a pressing need to explore safer and innovative drugs derived from plants or microbes, hailing from untapped biological resources. This approach is a promising way forward to address the critical healthcare challenges faced by the pharmaceutical sector [9-11]. Endophyte biology is imminent scientific domain which satisfies the needs of international pharma industry and produces a diversified group of bioactive compounds.

Multidisciplinary research methodologies and the analysis of a multitude of metabolites in the exploration of endophytes are still in their early stages, with only a handful of successful endeavors observed in the development of commercial applications for bioactive compounds synthesized by endophytic fungi. Consequently, the biotechnological utilization of fungal endophytes has become crucial in the fields of agriculture and industry, particularly in the extraction of valuable natural plant products. In this chapter, we delve into the pharmacological attributes of secondary metabolites originating from endophytic fungi that are isolated from medicinal plants.

FUNGAL ENDOPHYTES AS A TREASURE FOR BIOACTIVE COMPOUNDS

The search for novel pharmaceutical drugs derived from the secondary metabolites of microbes began in 1928, followed by the discovery of the antitumor drug Taxol, obtained from Taxomyces andreanae, and penicillin, isolated from Penicillium notatum by W. Flemming [Strobel et al., 1993]. These breakthroughs originally stemmed from Taxus brevifolia and Taxus wallichiana, which serve as hosts to endophytic fungi, namely Microspores of Taxomyces andreanae and Pestalotiopsis [Strobel et al., 1996]. This marked the dawning of a new era in the pursuit of naturally sourced drugs. The secondary metabolites produced by these fungal endophytes, endowed with antimicrobial properties, play a pivotal role in their effectiveness against pathogens that have developed resistance to antibiotics.

However, the synthesis and release of these secondary metabolites by fungal endophytes are subject to a multitude of influences, encompassing the timing of sample collection, environmental conditions, the plant's specific habitat (ranging from saline environments to high-altitude regions, rainforests, deserts, swamps, and marshes), nutrient availability, host plant tissues (such as roots, leaves, and seeds), and the type of plant species involved (including both angiosperms and gymnosperms) [Gupta et al., 2020; Aldinary et al., 2021].

Recent scientific literature has unveiled the remarkable ability of the endogenous fungus Alternaria sp to secrete bioactive compounds with cytotoxic, antitrypanosomic, and antisamaniotic properties. Notable compounds include Cladospirone B, Palmarumycin C6, 1, 4, 7β-trihydroxy-8-(spirodioxy-10, 80-naphthyl)-7,8-dihydronaphthalene, and Palmarumycin [Shan et al., 2014]. Furthermore, endogenous bacteria have demonstrated their capacity to produce a variety of bioactive compounds employed across pharmaceuticals, food, cosmetics, and agriculture. The secondary metabolites generated by these endophytes fall into various functional groups, including alkaloids, terpenoids, steroids, polyketones, peptides, flavonoids, furandiones, quinols, perylene derivatives, depsipeptides, and xanthones [Sharaf et al., 2022; Omojate Godstime et al., 2014].

Endophytic fungi a valuable resource of secondary metabolites

Compound	Endophytic fungi	Host plant	Reference	Reference
Dicerandrol A, B and C	*Phomopsis longicolla*	*Dicerandra frutescens*	Wagenaar and Clardy (2001)	Wagenaar and Clardy (2001)
Phomol	*Phomopsis* sp.	*Erythrina crista-galli*	Weber *et al.* (2004)	Weber *et al.* (2004)
Two Fusarusides	*Fusarium sp.*	*Quercus variabilis*	Shu *et al.* (2004)	Shu *et al.* (2004)
Fusapyridon A	*Fusarium sp.*	*Maackia chinensis from* Gottingen (Germany)	Tsuchinari *et al.* (2007)	Tsuchinari *et al.* (2007)
Fusaric acid	*Fusarium sp.*	Mangrove plant	Pan *et al.* (2011)	Pan *et al.* (2011)
Rhein	*Fusarium solani*	*Rheum palmatum* from Ruoergai County, China	Tegos *et al.* (2002)	Tegos *et al.* (2002)

Epoxydine	*Phoma sp.*	*Salsola oppostifolia*	Qin et al. (2010)	

Pentaketide	*Fusarium*	Selaginella pallescens	Brady and Clardy (2000)	
Glucoside derivatives – xylarosides	*Xylaria*	*Sordaricin*	Pongcharoen *et al.*(2008)	
Cytosporone B and C	*Phomopsis sp*	Mangroves	Huang *et.al.* (2008) .	
Cryptosporiopsis quercin	*Tripterigeum wilfordii*	Eurasia	Strobel and Daisy (2003)	
Colletotric acid	Colletotrichu m gloeosporioid es	Artemisia mongolica	(Zou et al., 2000)	**Reference**
Cytosporones D,	Cytospora sp. and Diaporth e sp.	Conocarpu s erecta and Forster onia spicata	(Brady et al., 2000)	Wagenaar and Clardy (2001)
Pestalone	Pestalotia sp.	Cocultured endophytic algal marine fungus/ marine bacterium strain CNJ328	(Cueto et al., 2001)	Weber *et al.* (2004)
Dicerandrols A, B and C	Phomopsis longicolla	Dicerandra frutescens	(Wagenaar and Clardy, 2001)	Shu *et al.* (2004)
Phomol	Phomopsis sp.	Erythrina crista-galli	(Isaka et al., 2001)	Tsuchinari *et al.* (2007)
Periconicins A and B	Periconia sp	Taxus cuspidate	(Weber et al., 2004)	Pan *et al.* (2011)
Monomethylsuloc hrin, Rhizoctonic acid, Ergosterol, 3β, 5α, 6β - trihydroxy ergosta- 7, 22 - diene	Rhizoctonia s p.	Cynodon dactylon	(Ma et al., 2004)	Tegos *et al.* (2002)
1- (2,6-dihydroxy phenyl) butan -1 - one. Sideritis chamaedryf olia 1-hydroxy -5- methoxy naphthalene, 1,5- dimethoxy -4- nitronaphthalene,	Coniothyrium sp	Sideritis chamaedryf olia	(Dai et al., 2006)	
Dinemasones A, B	Dinemaspori um strigosum	Calystegia sepium	(Krohn et al., 2008)	
Chaetoglobosin B	Chaetomium globosum	Viguiera robusta	(Momesso et al., 2008)	
7-amino -4- methyl coumarin	*Xylaria*	Ginkgo biloba	(Liu et al., 2008)	
Monocerin, (12S) -12-Hydroxy monocerin, Isocoumurin	Microdochiu m bolleyi	Fagonia cretica	(Zhang et al., 2008)	
Pseurotin A	Penicillium	Prumnopity s	(SchmedaHirschman n et al., 2008)	

	janczewskii	analina	
Ambuic acid	Pestalotiopsis sp.	Clavaroids sp.	(Ding et al., 2009)
Spiropreussione A	Preussia sp	Aquilaria sinensis	(Chen et al., 2009)
Xanalteric acids I and II, Altenusin	Alternaria sp	Sonneratia alba	(Kjer et al., 2009
Nodulisporins DF, benzene- 1, 2, 3 - triol	Nodulisporiu m sp.	Erica arborea	(Dai et al., 2009)
Pyrrocidine A	Acremonium zeae	Zea mays	(Wicklow and Poling, 2008)
Fusi di lactones D, E	Fusidium sp	Mentha arvensis	(Qin et al., 2009)
Javanicin	Chloridium s p.	Azadiracht a indica	(Kharwar et al., 2009)
Alterporriol D, Alterporriol E, Alterporriol N	Stemphylium globuliferuma n	Mentha pulegium	(Debbab et al., 2009)

BIOMEDICAL APPLICATIONS OF FUNGAL ENDOPHYTES

Antibacterial activity:

In a study conducted by Sanjeevan et al. in 2023, eight species of endophytic fungi were identified within G. repens. X.fejeensis was specifically examined for its production of specialized metabolites. These metabolites were isolated from the culture filtrate and identified as four known compounds, including 6', 7'-didehydro-total acid, 13-carboxy-total acid, and holistic acid. Of these, integrin acid was isolated and assessed for its antibacterial activity using a disk diffusion test against S. aureus, B. cereus, E. coli, and P. aeruginosa. The Minimum Inhibitory Concentration (MIC) was found to be 16 µg/ml against B. subtilis, a methicillin-resistant strain [Zizhong Tang et al., 2020].

In another study by Zizhong Tang and colleagues in 2020, 21 endophytic fungi were isolated from wild Conyza blinii. Among these isolates, six strains were found to produce flavonoids, with CBL11 secreting the highest total flavonoid content, reaching 50.78 ± 2.4 mg/L. The antimicrobial activity of CBL9 extracts was evaluated against E. coli, S. aureus, B. subtilis, and Pseudomonas. The most significant effect was observed against Escherichia coli, with an inhibition zone diameter of up to 24.67 ± 1.15 mm. Additional inhibition zone diameters for CBL9 were as follows: S. aureus (19.67 ± 2.52 mm), Bacillus subtilis (23 ± 2 mm), and Pseudomonas aeruginosa (17.33 ± 2.08 mm). Furthermore, CBL12, CBL12-2, and CBL1-1 exhibited remarkable antioxidant activity. Notably, CBL12 exhibited high radical scavenging rates for DPPH and ABTS, with values of 94.56 ± 0.29% and 99.88 ± 0.27%, respectively. Its IC50 values were a mere 0.11 ± 0.01 mg/mL and 0.2 ± 0.01 mg/mL [Zizhong Tang et al., 2020]. In a separate research endeavor led by Hiran Kanti and colleagues in 2022, a multitude of potent secondary metabolites were isolated from Cochliobolus sp. APS1, an endophyte of Andrographis paniculata. The primary compound among them was the alkaloid Aziridine, 1-(2-aminoethyl)-, which exhibited antibacterial, anti-biofilm, and anti-larval activities. The ethyl acetate culture filtrate displayed MIC and MBC values ranging from 15.62 to 250 µg/mL against 10 pathogenic bacteria, including MRSA and VRSA. Data related to killing kinetics, along with the leakage of macromolecules into the extracellular environment, support the bactericidal activity of these antibacterial principles [Hiran Kanti et al., 2022].

A total of 113 endophytic strains were isolated from a leaf and steam samples of *Zanthoxylum simulans* and cultured, among which 23 were found to possess antimicrobial activity which belongs to 6 fungal genera: *Penicillium* (26.09%, 6), *Colletotrichum* (21.74%, 5), *Diaporthe* (21.74%, 5), *Daldinia* (17.39%, 4), *Alternaria* (8.70%, 2), and *Didymella* (4.34%, 1). In addition, fungal endophytes produce antimicrobial agents, which may protect their hosts against pathogens and could be a potential source of natural antibiotics and their compositions differed between summer and winter[Jimmy Kuo et.al., 2021. In an another study Hongying Wu et.al., 2020 a total of 26 endophytic fungi were isolated, and out of which 21 isolates were identifiedandclassifiedinto8differentgenera,whichincludes *Briansuttonomyces*, *Glomerella*, *Pleosporales*, *Diaporthe*, *Phoma*, *Penicillium*, *Periconia and Colletotrichum.* The extract of *Penicillium* sp. exhibited greater potential for antibacterial activity, with the minimum inhibitory concentration (MIC) values against seven bacteria ranging from 1.25 to 6 mg/mL. The ethyl acetate extract of the *Diaporthe phaseolorum* Stdif6 displayed the most significant antifungal activity against all tested phytopathogens, with EC50 values ranging from 0.0138 to 0.3103 mg/mL [Hongying_Wu*et.al.*, 2020].

Extracts from five different endophytic fungi, coded as CR-MR1B, CR-MR1, CR-MR3, CR-MRB2, and CR-LC, isolated from pink catharanthus, demonstrated substantial antibacterial activity against various microorganisms. CR-MR1 exhibited inhibition against S. typhi, E. coli, A. fumigatus, and C. albicans, while S. aureus and B. subtilis were not affected. CR-MR1B displayed a MIC of 1 mg/mL against S. aureus, B. subtilis, S. typhi, and A. fumigatus, with a MIC of 0.5 mg/mL for C. albicans. CR-MRB2 had a MIC of 1 mg/mL against B. subtilis only. CR-MR3 demonstrated a MIC of 0.25 mg/mL against S. aureus, B. subtilis, S. typhi, C. albicans, and E. coli, with a MIC of 0.5 mg/mL for A. fumigatus. CR-LC exhibited MICs of 0.0625 ng/mL against S. aureus, 0.03125 mg/mL against B. subtilis, 0.25 mg/mL against S. typhi, and 0.125 mg/mL against E. coli. However, neither A. fumigatus nor C. albicans exhibited inhibition at any concentration. Consequently, CR-LC and CR-MR3 demonstrated antibacterial properties, while CR-MR1 and CR-MR1B hold promise for further development as antifungals [Akpotu et al., 2017].In another study by Abba et al. in 2018, endophyte pseudofusicoccum spp. isolated from Anona muricata exhibited moderate antibacterial activity. It inhibited B. subtilis at a concentration of 1 mg/mL, with inhibition zone diameters (IZDs) of 2 mm, 3 mm, and 2 mm against S. typhi, and C. albicans, respectively. However, it did not inhibit S. aureus, E. coli, and A. niger. The standard drug, ciprofloxacin, at a concentration of 50 µg/mL, inhibited all tested organisms with IZDs ranging from 5 to 14 mm [Abba et al., 2018]. Furthermore, an extract from Psidium guajava, labeled as HA-labeled endogenous fungal extracts, demonstrated antibacterial activity against pathogenic microorganisms. At a concentration of 1 mg/mL, HA inhibited all tested organisms, including E. coli, S. aureus, B. subtilis, and S. typhi, with IZDs of 5 mm, 6 mm, 5 mm, and 4 mm, respectively. However, GA exhibited an IZD of 7 mm against S. aureus [Author Name et al., Year].

Antifungal activity:

In one study conducted by Tejesvi et al. in 2007, a total of 32 ethyl acetate extracts collected from Pestalotiopsis spp. isolated from four medicinal plants, namely Azadirachta indica, Holarrhena antidysenterica, Terminalia arjuna, and T. chebula, were quantitatively evaluated for their antifungal activity by observing the presence or absence of inhibition zones. Among these extracts, 20 (62.5%) isolates exhibited significant antifungal activity against a range of pathogenic fungi. The maximum inhibitory zone was observed against Alternaria carthami, Fusarium verticilloides, and Phoma sorghina, with inhibitory zones ranging from 4 to 25 mm. Notably, isolates 4, 9, 11, and 15 displayed significant inhibitory zones, while fewer inhibitory zones were observed for the isolates obtained from Terminalia chebula, Azadirachta indica, and Holarrhena antidysenterica, isolated from different locations, across all tested fungi [Tejesvi et al., 2007].In a separate scientific study conducted by Hong Wing et al. in 2020, over 25 fungal endophytes were isolated from the medicinal plant Stephania dielsiana and classified into eight different genera, including Briansuttonomyces, Glomerella, Pleosporales, Diaporthe, Phoma, Penicillium, Periconia, and Colletotrichum. Among these isolates, the ethyl acetate extract of Diaporthe phaseolorum exhibited the most significant antifungal activity against phytopathogens, with EC50 values ranging from 0.0138 to 0.3103 mg/mL [Hong Wing et al., 2020].Noha Kamel et al. in 2019 isolated 22 different fungal species from various plant parts of Euphorbia geniculata and categorized them into 15 fungal genera. Aspergillus was the most frequently isolated genus. They evaluated the antimycotic activity of these isolates against common fungal pathogens such as Eupenicillium brefeldianum, Penicillium echinulatum, Alternaria phragmospora, Fusarium oxysporum, Fusarium verticilloides, and Alternaria alternata in dual culture assays. Their findings showed that Aspergillus flavus, A. fumigatus, and Fusarium lateritium exhibited the highest antagonistic activity, while Cladosporium herbarum, F. culmorum, and Sporotrichum thermophile exhibited the lowest antagonistic activity. They also noted elevated levels of secondary metabolites, especially terpenes and alkaloids, in comparison to their host E. geniculata. These secondary metabolites were extracted using organic solvents like ethyl acetate and n-butanol from all six endophytes and evaluated for their antimycotic activity at three different concentrations (0.5, 1.0, and 2.0 mg/mL) against three pathogenic fungi, E. brefeldianum-EBT-1, P. echinulatum-PET-2, and A. phragmospora-APT-3, which were isolated from tomato plants, and they exhibited promising antifungal activity [Noha Kamel et al., 2019].

In another study led by Xingli Zhao et al. in 2020, 183 isolates were classified into 13 genera based on their morphological features and internal transcribed spacer sequence analysis. Among these, Alternaria, Botryosphaeria, and Talaromyces were dominant communities. Dual culture studies were employed to evaluate their antifungal activity against the four primary fungal pathogens of C. officinalis for 75 representative endophytes. The study found that nine strains exhibited antibiosis, and eight strains displayed an inhibition rate of over 50% [Xingli Zhao et al., 2020].

Antiviral activity:

The urgent need for the development of novel antiviral drugs arises from the growing concern over microbial resistance to antibiotics. Endophytic fungi offer a promising avenue for researchers as they provide opportunities for the isolation, identification, and purification of secondary metabolites, which may serve as potential candidates for the development of antiviral drugs. This field of study has garnered significant interest due to the limited knowledge available, making it a captivating area of research. However, the development of antiviral compounds faces several challenges, primarily

linked to the inefficiency and inadequacy of antiviral screening methods in many metabolite discovery programs. It is worth noting that numerous metabolic compounds derived from endophytic organisms have shown potent antiviral properties against a variety of human infecting viruses, including HIV (Human Immunodeficiency Virus), cytomegalovirus, and H1N1 influenza A virus. These findings highlight the potential of endophytic fungi in the search for effective antiviral agents [Farooq et al., 2016; Raekiansyah et al., 2017; Liu et al., 2019].

In a study conducted by Han et al. in 2019, Trichoderma harzianum SWUKD3.1610 was isolated from Kadsura angustifolia, and a compound with the same TLC Rf value and HPLC retention time as authentic nigranoic acid was identified. This compound exhibited exceptional antiviral activity by inhibiting the reverse transcriptase enzyme in HIV-1. Another promising discovery was made when an ethanol extract of Curvularia papendorfii, an endophytic fungus isolated from Vernonia amygdalina, a medicinal plant from Sudan, displayed antiviral activity against two human viral pathogens: coronavirus HCoV 229E and a norovirus surrogate, the feline coronavirus FCV F9. At a lower multiplicity of infection (MOI) of 0.0001, a 40% reduction in virus-induced cytopathogenic effect was observed [Afra Khirala et al., 2020]. Si-si Liu et al. in 2018 isolated a rare 14-nordrimane-type sesquiterpenoid named phomanolide, along with five other known compounds, from the culture filtrate of an endophytic fungus, Phoma sp., isolated from the roots of Aconitum vilmorinianum. These compounds exhibited antiviral activity with IC50 values of 2.96 ± 0.64 μg/mL against the influenza virus (A/Puerto Rico/8/34, H1N1).Furthermore, in a study by Raekiansyah et al. in 2017, antiviral substances were investigated in the extracts of the Penicillium sp. FKI-7127 strain. The researchers identified brefeldin A as a novel antiviral compound with activity against dengue viruses of various serotypes, as well as other related viruses such as Zika virus and Japanese encephalitis virus. Brefeldin A exerts its antiviral effect at an early stage of the dengue virus (DENV) life cycle [Raekiansyah et al., 2017].

3.4. Anti- diabetic activity:

Numerous natural resources offer abundant opportunities for harnessing their potential in therapeutic applications [62]. Diabetes, a metabolic disorder characterized by elevated blood glucose levels due to insufficient insulin production or an inadequate response of the body's cells to insulin [63], presents a growing global health challenge. Traditional chemotherapy may entail undesirable side effects for diabetic patients. Consequently, ongoing research endeavors aim to discover effective anti-diabetic drugs derived from microorganisms. In light of these circumstances, there is a pressing need for the development of novel and alternative therapies with minimal or no side effects. As a result, numerous researchers have documented the anti-diabetic and anti-lipidemic properties of secondary metabolites derived from fungal endophytes [66].

In a study conducted by Singh and Kaur in 2016, thirty-six endophytic fungi were isolated from Acacia nilotica and screened for their ability to produce metabolites with enzymatic inhibition properties against both alpha-amylase and alpha-glucosidase. Among the isolates, Aspergillus awamori demonstrated the capacity to produce an inhibitory substance, which was subsequently purified using Sephadex LH-20 column and semi-preparative HPLC methods. This substance was identified as proteinaceous in nature with an approximate molecular weight of 22 kDa. It exhibited remarkable inhibition against both alpha-amylase (81%) and alpha-glucosidase (80%), with IC50 values of 3.75 and 5.625 μg/ml, respectively.Additionally, Ye et al. in 2021 isolated ten alkaloids, including six new diketopiperazine alkaloids, from the endophytic fungus Aspergillus sp. 16-5c, obtained from mangrove plants. The structure of these new compounds was identified through 1D/2D NMR spectroscopic and HR-ESIMS data analyses. The antidiabetic activity of these compounds was evaluated against α-glucosidase and PTP1B enzyme. Results from the bioassay revealed that compounds 1 ($C_{21}H_{25}O_3N_3$) and 9 (brevianamide K) exhibited significant inhibitory activity against the α-glucosidase enzyme, with IC50 values of 18.2 and 7.6 μM, respectively. Compounds 3, 10, 11, and 15 displayed moderate α-glucosidase inhibition, with IC50 values ranging from 40.7 to 83.9 μM, while no compounds exhibited significant PTP1B enzyme inhibition.Furthermore, Govindappa et al. in 2015 reported on Alternaria spp, an endophyte isolated from Viscum album, which had the ability to secrete a lectin compound (N-acetyl-galactosamine) into the extracellular environment. This compound, a 54 KDa protein molecule, was partially purified and assessed for its anti-diabetic efficacy in vitro and in vivo. It demonstrated robust antidiabetic activity in both scenarios, strongly inhibiting three significant diabetic enzymes, namely α-amylase (85.26 ± 1.25), α-glucosidase (93.41 ± 1.27), and sucrase (81.61 ± 1.05) [Govindappa et al., 2015].

In a separate investigation,researchers identified an endophytic fungal metabolite capable of activating the insulin receptor, specifically the tyrosine kinase, a non-peptidal fungal metabolite known as L-783,281. In vitro assessments of this compound following oral administration resulted in a significant reduction in blood glucose levels [Zhang et al., 1999]. These findings have paved the way for the discovery of novel receptor activators for insulin protein, holding promise for the development of innovative diabetes therapies.Furthermore, in another study, three biosynthetic compounds were partially purified from the culture filtrates of Nigrospora oryzae, an endophyte isolated from

Combretum dolichopetalum leaves. These compounds, namely (S)-(+)-2-cis-4-trans-abscisic acid (1), 7'-hydroxy-abscisic acid (2), and 4-des-hydroxyl altersolanol A (3), were evaluated for their potential antidiabetic properties in vitro using alloxan-induced diabetic mice. The study involved monitoring their fasting blood sugar levels for 9 hours, and it was observed that these compounds significantly ($p<0.001$) reduced fasting glucose levels in diabetic mice [Philip et al., 2017].The authors also noted that β-amylase inhibitors had a significant impact on reducing the glucose content of complex carbohydrates and slowing glucose absorption. Previous reports have highlighted the screening of endogenous fungi as potential sources of alpha-glucosidase inhibitors [89], including Fusarium spp. and Alternaria spp. These findings underscore the multifaceted potential of some fungal endophytes as valuable sources of pharmaceutical compounds, including those with antidiabetic properties.

Future Aspects:

Recent scientific literature on plant associated fungi (Endophytic fungi) has exposed their wide ecological distribution, its bio-diversity and multidimensional interactions with its host organisms and other micro biome in the symbiotic range. The specific relation between endophytic fungi and its host had lead to the generation of numerous compounds which can be categorized in too many groups; each can exhibit a broad range of effects against number of pathogens. Exploration of the uncharted realm of plant-associated microorganisms represents an intriguing and auspicious avenue for offering solutions in the realms of agriculture, pharmaceuticals, and medicine. Scientists have increasingly turned their focus to the potential utility of endophytes found in medicinal plants, examining their secondary metabolites with significant pharmacological promise.

- Relationship among newly introduced endophytes and inhabitant plant endobiome.
- Limited knowledge on plant-endophyte communications, chemical agents which suppress the plant immune response, regulation of gene expression, and signaling pathway (Ma *et.al.* 2016, 2019).

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