Endophytic fungi and their diversified applications

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Abstract

Endophytic fungi survive a part of their lifespan inter or intracellularly in plants without causing any damage. The group of diversified microorganisms comprising filamentous fungi and yeasts, are also capable of increasing agricultural productivity. Medicinal plants that have been used as a complementary form of medicine since ancient time are a significant source of endophytes in bioprospecting. Each part of the medicinal plant, including the roots, stem, leaves, fruits, flowers, bark, scales, resin canals, and even the meristem, has been screened for endophytes. Endophytic fungi from medicinal plants becomes a rich source of bioactive and chemically unique chemicals. Some of the endophytic fungi such as *Acremonium*, *Alternaria*, *Apiospora*, *Aspergillus*, *Aureobasidium*, *Bartalinia*, *Cephalosporium*, *Chaetomium*, *Chloridium*, *Choanephora*, *Colletotrichum, Cryptosporiopsis, Emericella, Eupenicillium, Eutypella, Eutypella, Fusarium, Gliocladium, Hypoxylon, Paecilomyces, Penicillium, Pestalotiopsis, Pseudomassari, Quercina, Talaromyces,* and *Trichoderma* have been stated from various medicinal plants. Endophytic fungi produce a variety of bioactive metabolites, including terpenoids, steroids, quinones, phenols, coumarins, and others, that come from several metabolic routes. They are used in the pharmaceutical and agrochemical industries for its anticancer, immunomodulatory, antioxidant, antiparasitic, antiviral, antidiabetic, antitubercular, insecticidal activity. In this review endophytic fungi having significant potential in pharmacological field have been listed and summarized. This will give insight for further research on exploring properties of endophytes.

Keywords : Bioactive compounds, Biodiversity, Endophytic fungi, Secondary metabolites

1. Introduction

Endophyte term was created by German botanist Anton de Barry in 1866 where the "endo**"** represents "within**"** and **"**phyton**"** means "plant"**.** Endophytic fungi are a group of endosymbiotic microorganisms present asymptomatically inside the internal tissues beneath the epidermal cell layer of healthy living plants such as stems, roots, leaves, bark, and scales without significant morphological changes to the host plants (pirttial et al.,2008)**.** The endophytic microbes provide nutrients to the plant as well as defense against abiotic and biotic stress. Endophytic microorganisms that live inside plant tissue include bacteria, fungi, viruses, and protozoa. (Hyde and Soytong 2008; Rodriguez et al. 2009; Hardoim et al. 2015) but the presence of fungi is abundant. Among 1.5 million different species of fungi present over the land, one million are endophytic fungi i.e., one or more endophytic fungus species present in every single plant in nature (Strobel and daisy,2003), (stone et al.,2004; demain,2014)**.** Biological diversity occurs naturally in temperate regions and tropical rainforests in the case of the endophytic fungi. They colonize at their site of presence and can be easily isolated in a microbial growth medium. Endophytic fungus and their host may have a mutualistic, antagonistic, or parasitic relationship. They produce diversified metabolites of biotechnological interest which can be further useful in the field of agriculture, industry, and the healthcare sector (Ruma et al., 2013). The endophytes act as a reservoir of novel bioactive secondary metabolites such as alkaloids, terpenoids, steroids, peptides, phenol, xanthones, quinones, and flavonoids (Zhanget al., 2006).

In economically developing countries about 80% of people use herbally formulated medicine products rich in natural bioactive products which are vital for the prevention of many diseases (Pan et al., 2013; Yirga et al., 2011) with lesser or no side effects. Almost 70% of the existing bioactive compounds are synthesized from different microorganisms so the upcoming research involving endophytic fungi for the isolation of various useful compounds is noteworthy.

Further studies are needed to meet the demand for endophytes for useful compounds and understand the pathogenic activity associated with human health and other medical uses. So, in the present review, the role of endophytic fungi in treating various diseases along with their mechanism is briefly discussed. Finding novel bioactive chemicals from endophytic fungi will now have a new direction.

2. Isolation and characterization of endophytic fungi

Fungi are important components of an ecosystem that are crucially associated with the process of transportation of nutrients, recycling, and degradation. Endophytic fungi are found in small amounts and limited locations inside the plant. Isolation of endophytic fungi from different parts of a plant such as stems, roots, leaves, flowers, meristems, barks and shoots and the isolation process start with sterilization of the surface of the explant to prevent contamination by unwanted microorganisms. Explants are later sterilized by immersing in 70% ethanol for 1-3mins, 1-3% sodium hypochlorite for 3-5 mins and repeatedly washing with distilled water, inoculation under desired media and incubating for a week.

The characterization and identification of endophytic fungi, morphological classification of fungi based on colour, size of spores, colony diameter, texture, shape, and growth rate. The characterization of fungi by molecular techniques includes genomic isolation, genome sequencing of desired genes, and amplification of a gene of interest for the taxonomical and phylogeny relationship by PCR. The preservation of fungi for long-term uses is to subculture onto fresh media or preservative of spores and mycelium into 20% glycerol in (w/w) and stored at -80*C.

3. Biodiversity and distribution of fungal endophytes

Recent studies report nearly 300,000 plant species on our planet each plant consists of one or more endophytes (Strobel and daisy 2003), creating extensive biodiversity. They can isolate from different healthy medicinal plants. In recent times study has revealed an abundance of endophytic fungal species and distinct metabolite with different metabolisms which provide essential information for fungal diversity, the discovery of new species and ecological distribution as well as biotechnological potential (Zimmerman and Vitousek 2012; Xiao et al. 2014; Zhang et al. 2014a, b). The solubilization of the macronutrient phosphorus, potassium, and zinc, the fixation of atmospheric nitrogen, and the production of different hydrolytic enzymes, ammonia, siderophore, and hydrogen cyanide are all made possible by endophytic fungi. They also play a substantial role in defending their host from attack by phytopathogens (HCN) (Maheshwari 2011; Rana et al. 2016a, b, 2017; Verma et al. 2015b, c, 2016a, b). *Ascomycota*, *Basidiomycota*, and *Mucoromycota*, among other phyla, are among the reported fungi, according to a study of the diverse research on the diversity of endophytic fungi. Endophytes are a novel source for the production of natural bioactive compounds for various purposes in agriculture, and medical applications (Storbel et al.

2014). The diversity and quantity of endophytic fungi found in both leguminous and nonleguminous crops such as wheat, tomato, and rice, soybean, pigeon pea, chickpea, common pea, maize, and other plant species. Endophytic fungi produce some of the most broadly used antibiotics and antidrug such as penicillin, extracted from *Penicillium* sp., which is cytotoxic to numerous cell lines, Taxol isolated from *Taxomyces andreae*, is the most effective and extraction of drugs from endophytic fungi such as clavatol, sordaricin, and javanicin are all known for strong antifungal and antibacterial properties against various infections (Toofanee ad Duly-mamode, 2002). endophytic microorganisms from 17 different host plants show the diversity of endophytic fungus found in these various hosts. Fungal endophytes like *Alternaria* sp., Cladosporium sp., Davidella sp., Diaporthe sp., Epicoccum sp., Fusarium sp., Phialophora sp., Phoma sp., Phomopsis sp., Plectosphaerella sp., Trichoderma sp., and Verticillium sp. on soybean plants were discovered by culture (Impullitti and Malvick 2013; Tenguria and Firodiya 2013). Endophytic fungi from fresh *Glycine max* leaves collected from the central region of Madhya Pradesh, India, marked presence of *Acremonium sp*., *Alternaria alternate*, *Aspergillus sp*., *Colletotrichum sp*., *Emericella nidulans*, *Fusarium sp*., *Penicillium sp*., and *Phoma sp.* (Fernandes et al. 2015). Several studies have reported that *Alternaria sp.* from *Catharanthus roseus* are known for the synthesis of bioactive compounds like alkaloids, vinblastine, and dendryphionnanum from *Ficus religiosa* produce antidiabetic compound (Mishra et al., 2013), *Aspergillus niger* from *Taxus baccata* produces lovastatin (Raghunath et al., 2012), *Colletotrichum gloeosporioides* from *Forsythia suspensa* produces phillyrin (Zhang et al., 2012), Endophytic fungus Stachybotrys chartarum produces chartarlactams A-P and phenylspirodrimanes which reveal vigorous antihyperlipidemic activity (Li et al., 2014b), Aspergillus flavus (Host Aegle marmelos) produces bioflavonoid (Patil et al., 2015), *Aspergillus niger* and *Alternaria alternata* from *Tabebula ar-gentea* produces lapachol (Sadananda et al., 2011).

In the current scenario, the uncontrol and inadequate utilization of chemical fertilizers and pesticides, whether directly or indirectly may lead to cause environmental damage and human health. Endophytes have the potential to produce phytohormones such as auxin, gibberellin (GAs), and cytokinin which are the alternatives process that could use to replace chemical utilization for sustainable development (Carneiro et al. 2015; Ahmad et al. 2018). These molecules have a vital role in signalling and messaging plant growth in different climatic conditions. Primary auxin isolated from fungi indole-3-acetic acid (IAA). They regulate plant growth with a beneficial impact on roots and shoot development which gives responses to cell elongation, division, and differentiation of vascular tissues which initiates root formation (Jaroszuk-Ściseł et al. 2014). The endophytic fungi Phoma glomerate and Penicillium sp. were reported by (Waqas et al. (2012) production of IAA and GAs. The fungal endophyte *Paecilomyces formosus* strains LHL10 from cucumber plant roots which promote plant growth with the production of IAA and Gas (Khan et al. 2012). Gibberellins are essential for some plant responses including seed germination, stem elongation, sexual expression, flourishing, fruit formation and senescence (Bömke and Tudzynski 2009). Production of bioactive gibberellins GA1, GA3, GA4, and, GA7 were extracted from *Gibberella fujikuroi*, which was used as a control for GA production. The final products of gibberellins as acetyl-coa from mevalonic acid pathway (MVA) are GA1 and GA3 produced from GA4, GA5, and GA7 (Bömke et al. 2008; Khan et al. 2008, 2015), for example, the endophytic fungi *Phoma sp*. GAH7 was isolated from the roots of the cucumber, which produced an abundance of GA3, GA4, GA9, and GA19 (Hamayun et al. 2010). *Aspergillus fumigatus* (strain HK-5-2) were described for the production of gibberellins (Hamayun et al. 2009a), *Cladosporium sphaerospermum* with strain DK-1-1 (Hamayun et al. 2009b), used to improve the plant growth of soybeans.

4. Pharmaceutical applications

Endophytic fungi possess a eukaryotic system which is capable of producing bioactive compounds which is the promising source in pharmaceutical applications with the help of the production of secondary metabolites. Endophytic fungi have a novel resource for drug discovery to overcome the increasing level of human pathogens. Fungal endophytes have various biochemical and biological properties which are useful for various diseases. Endophytes can produce several extracellular enzymes such as pectinase, cellulase, lipase, protease and amylase (Jordaan et al. 2009; Borges et al. 2009; Rajulu et al. 2O11; Bezerra et al 2012). It can also produce many secondary metabolites or bioactive compounds which were synthesized by the plant. The secondary metabolites are mainly categorized into various functional groups such as steroids, flavonoids, alkaloids, terpenoids, phenol, quinones, xanthones, Taxol, etc (Stierel et al. 1993; Li et al. 2000; Barrosand Rodrigues-Filho 2005; Yin et al. 2009; Kumar et al. 2013; Soliman et al 2013). Microbes served as an important source of drug treatment against diseases with potential applications in the fields of pharmaceutical, medical, food, and cosmetics industries. They are well known for synthesizing antibodies, anticancer, antioxidant, antimicrobial, and antidiabetic, cytotoxicity, and other important biological compounds (Kharwar et al. 2011a; Sun et al. 2011; Akay et al. 2014; Xiao et al. 2014; Zhou et al. 2014a, b).

4.1. Endophytic Fungi as an anti-cancer Agent

Cancer is one of the major hazardous diseases around the world, caused by uncontrolled division and growth of cells due to mutations. Every year more than 6 million cases are registered. Endophytic fungi have incredible chemical diversity found in millions of species of plants; plant derivate compounds played a vital role in the development of various clinically useful anticancer agents these include vinblastine, camptothecin, vincristine, podophyllotoxin, and taxol (Balunas and Kinghorn, 2005). Taxol (also known as paclitaxel) is the world's first anti-cancer drug (a diterpenoid) isolated from Taxomyces Andreae in 1993 (Sterle et al. 1993) from the bark of the pacific yew tree (Taxus brevifolia) (Wani et al. 1971). Supply of taxol from the bark is restricted (Wheeler et al. 1992) due to the slow growth of the plant as it takes decades to grow a few inches (Flores and Sgrignoli 1991), as removal of bark results in the death of the plant (Kwak et al. 1995) and plants do not find in large quantity in nature. The food and Drug Administration (FDA), USA, has proved that taxol has been widely used for the clinical treatment of breast and ovarian cancer (Cremasco et al. 2009). Taxol represents a unique mode of action for Antineoplastic agents and antimicrotubular agents. Currently, it is also used for various clinical treatments such as gastric. renal, prostate, pancreatic, cervix, head, neck and colon cancers (Einzig et al. 1991; Arbucket al.1993). Numerous Taxus like Taxus canadensis, Taxus baccata, Taxus wallichiana, Taxus chinensis, Taxus x media, Taxus floridana, Taxus yunannensis, Taxus mairei, Taxus sumatrana, and Taxus cuspidata all suitable for the production of taxol (Majumder and Jha 2009). Several other anti-cancerous drugs are isolated from endophytic fungi such as 9-methoxycamptothecin and 10-hydroxy camptothecin from Fusarium solani, Phialocephala fortinii isolate compound podophyllotoxin, Entrophospora infrequent produces camptothecin, Aspergillus fumigatus produces deoxypodophyllotoxin, vinblastine and vincristine are dimeric alkaloids isolated from leaves of Madagascar periwinkle plant (Catharantus roseus) used in antineoplastic agents.

4.2. Endophytic fungi as an anti-oxidant agent

Antioxidant agents are used for the prevention of damage to the cells caused by unbalanced molecules known as free radicals and the relative presence of ROS (Reactive Oxygen Species).

These ROS are free radical, unstable molecules that build up volatile oxygen that easily reacts with or may cause damage to DNA, RNA, and proteins and sometimes lead to cell death. This results in a loss of electrons from an atom and may produce free radicals this chemical reaction Is known as Oxidation. Due to oxidative stress, the cells undergo cellular degradation like cancer, atherosclerosis, coronary heart ailments, diabetes, Alzheimer's disease, and hepatic and kidney failure as well as other neurodegenerative disorders. Abundant, use of antioxidants in the field of pharmaceutical industries, agrochemical industry, and food industries (Panigrahy et al. 2016). The endophytic fungi produce several antioxidants including phenolic acids, phenylpropanoids, flavonoids, lignin, melanin, and tannins and produce stress tolerance inside the host. Naturally occurring antioxidant CSA (Cajaninstilbene acid), 3-hydroxy-4-prenyl-5-methoxys-stilbene-2-carboxylic acid isolated from pigeon peas of endophyte Fusarium (Zhao et al. 2012a, b). About 41 endophytic bioactive compounds, Xylaria sp. isolated from Ginkgo biloba medicinal plant show various strong activities such as antioxidant, antimicrobial, anticancer, and anti-cardiovascular (Liu et al. 2007). Finding of several biomolecules as antioxidants such as Pestacin($C_{15}H_{14}O_4$), Isopestacin($C_{15}H_{12}O_5$), and 1,3-dihydro isobenzofurans isolated from endophytic fungi Pestalotiopsis microspore located in Terminalia morobensis shows strong efficiency of antioxidant activities.

4.3.Endophytic fungi as an anti-diabetic Agent

Diabetes Mellitus is one of the chronic disorders in the world. A recent statically study has reported that (DM) is speedily increasing globally and increasing health disorders. About 415 million people around the world are suffering from diabetes mellitus and it is predicted to be 629 million in 2024 (according to World Health Organization). This results in a deficiency of insulin secretion, and disturbance of metabolic activities by alpha-amylase such as fats, proteins, and carbohydrates. Several studies reveal that 90% of the population has type-2 Diabetes Mellitus which is related to a genetic disorder associated with low production of insulin. Alpha-amylase and alpha-glucosidase are 2 vital enzymes that are responsible for the hydrolysis of glucose molecules (saccharides) in the digestive system (Panigrahy et al. 2017). This Type II-DM is associated with health hazards such as cardiovascular disease, peripheral vascular disease, stroke, diabetic neuropathy, amputations, renal failure, and blindness (Panigrahy et al. 2021; Panigrahy et al. 2020). The drawback of insulin medication is very difficult to regulate the blood sugar level every day. The expanses of oral anti-hyperglycemic agents increasing day by day. So, endophytic fungi are the novel source of production of antidiabetic compounds which are alternatives to therapeutic treatment with fewer expenses. 90-95% of people suffer from the most common type of DM (Type II). *Cupressus torulosa* leaves were used to isolate *Penicillium Oxalicum*. The methanolic and chloroform organic extracts of this fungus showed exceptionally high levels of inhibitory activity against -amylase, with IC_{50} values of 46.73 and 59.20 g/mL, respectively. Moreover, the control acarbose reported an IC_{50} value for α-amylase of 26.76 g/mL in comparable experimental circumstances. *Ocimum sanctum* included the endophytic fungus *Alternaria tenuissima* and *Diaporthe sp.* With an IC_{50} value of 27.34 and 40.73, these fungal isolates ethyl acetate extracts showed the greatest in vitro inhibition of the pancreatic-amylase enzyme. Stemphylium globuliferum endophytic fungi were discovered in the fruit of Momordica charantia, an anti-diabetic herb. This fungus' ethyl acetate extract demonstrated encouraging inhibition of -amylase with an IC50 value of 13.48 g/ml.

4.3. Antimicrobial Activity

Many research has been directed at the antimicrobial properties of endophytic fungi isolated from various geographic locations. Long-term evolution typically results in plants developing the ability to protect themselves by producing a variety of secondary metabolites such alkaloids, terpenoids, steroids, and aromatic chemicals that are supposedly repulsive or even toxic to the "enemy". Low molecular weight organic, naturally occurring compounds known as antimicrobial agents are produced by microbes and have modest concentrations of activity against other germs (Guo et al. 2000). Maria et al. studied antifungal and antibacterial activities of 14 endophytic fungi isolated from two mangrove plants, viz. Acanthus ilicifolius and Acrostichum aureum L. indicated that many mangrove plant endophytes are likely to possess novel metabolites. Fifteen endophytes from eight medicinally significant plant hosts from India's Western Ghats have antibacterial potential (Raviraja et al. 2006). These endophytes grow on leaves, stems, and bark. Extracts from Alternaria species, Nigrospora oryzae, and Papulospora species that had been partially purified showed strong antimicrobial activities against particular bacteria and fungi. These discovered compounds show antifungal and antibacterial action against the plant pathogenic bacteria Xanthomonas campestris and Xanthomonas oryzae as well as the pathogenic fungi Fusarium oxysporum, Rhizoctonia solani, Colletotrichum gloeosporioides, and Magnaporthe oryzae (Wang et al. 2012). The rhizome of Paris polyphylla var. yunnanensis, a medicinal plant used in traditional Chinese medicine, contains a wide variety of endophytic fungi. It has been reported that endophytic Phoma sp. isolated from various medicinal plants is a prospective source of antibacterial substances. There have been reports of Phoma sp. producing a novel a-tetralone derivative (3S)-3,6,7-trihydroxy-a-tetralone, cercosporamide, b-sitosterol, and trichodermin as an endophytic in Arisaema erubescens. Similarly, it is known that Phoma sp., which is endophytic in Saurauia scaberrinae, produces Phomodione(62) ($C_{20}H_{22}O_8$) [(4aS*,9bR*)]. -2,6-diacetyl- \s7-hydroxy-4a,9-dimethoxy-8,9b-dimethyl-4a. A derivative of usnic acid, 9b-di-hydrodibenzo[b,d]furan-1,3(2H,4H)-dione. Staphylococcus aureus was found to be susceptible to phomodione, at least to an inhibitory level (Hoffman et al. 2008). Santiago et al. (2012) studied the bioactivity of the metabolites produced by the endophytic Phoma sp. of Cinnamomum mollissimum. It has been discovered that the fungal pathogen Aspergillus niger is inhibited by the polyketide molecule 5-hydroxyramulosin ($C_{10}H_{14}O_4$). The main terpenoids produced by endophytic fungi, which have antimicrobial activity, are sesquiterpenes, diterpenoids, and triterpenoids. The endophytic fungus Pichia guillermondii Ppf9 from Paris polyphylla var. yunnanensis yielded one terpenoid and three terpenoid chemicals. The substances were identified as helvolic acid, ergosta-5,7,22-trienol (65), 5a,8a-epid ioxyergosta-6,22-dien-3b-ol ($C_{28}H_{44}O_3$), and ergosta-7,22-dien-3b,5a,6b-triol ($C_{28}H_{46}O_3$) ($C_{32}H_{44}O_8$).

5. Miscellaneous activities

5.1. Nitrogen Fixation

Symbiotic and free-living microorganisms promotes plant growth due to their ability to biologically fix nitrogen by turning atmospheric nitrogen into ammonia (which plants may absorb) (Zhang et al., 2020). Free-living non-symbionts and endophytes, in contrast to the leguminous plant-rhizobial symbionts located in root nodules, have a different capacity to fix nitrogen. Rhizobial and actinorhizal plant symbionts, including species of Frankia, Azospirillum, and Rhizobia, were the main nitrogen-fixing organisms observed (Lindström and Mousavi, 2020). An exceptional bacterium with a high rate of nitrogen fixation is endophytic Gluconacetobacter diazotrophicus (Dong et al., 1994; Bertalan et al., 2009). It has been reported that many agricultural plants have been observed to fix nitrogen using free-living endophytes like Acetobacter diazotrophicus, Azoarcus, Herbaspirillum, Burkholderia, Bacillus, Acinetobacter, Methylobacterium, Enterobacter, Alcaligenes, Pantoea, and Klebsiella (Reinhold-Hurek and Hurek, 1998; Cocking, 2003). Endophytic Phomopsis liquidambri increases nodulation and nitrogen uptake in peanut plants via signalling with H2O2 and NO (Xie et al., 2017).

5.2. Phosphate solubilization

phosphorous places second ranked nutrient after nitrogen, endophytes' able to acquire nutrients through the solubilization of phosphate is crucial for stimulating plant growth. In soil, phosphorus naturally occurs in the mineral’s apatite, fluorapatite, and hydroxyapatite. They are undetectable to plants, although, due to their insolubility. Endophytic microorganisms use mechanisms such as adsorption and exchange, reducing pH, and acidification by the release of organic acids to solubilize both organic and inorganic forms of phosphorous. The primary mechanism involved in this process is the secretion of organic acids like lactic acid and acetic acid, which chelate the cations associated with phosphate and ultimately transform insoluble phosphorous into a soluble form. *Aspergillus*, *Penicillium*, and *Trichoderma* species of fungal endophytes, as well as endophytic mycorrhizal (EM) fungi, have all been found to effectively solubilize phosphate (Wakelin et al., 2004; Mehta et al., 2019). *Aspergillus*, *Penicillium*, and *Trichoderma species*, as well as arbuscular mycorrhizal (AM) fungi, have all been reported to effectively solubilize phosphate among endophytic fungi. In *Helianthus tuberosus* L., a synergistic interaction between EM fungus and phosphate-solubilizing bacteria has also been observed to significantly boost plant development (Rana et al., 2020).

5.3. Siderophore production

Certain microorganisms, such as endophytic fungi, create siderophores, which are tiny molecules with iron-chelation characteristics, to bind cupric ions in the rhizosphere (Chowdappa et al. Citation2020; Sr et al. Citation2020). Iron is an essential microelement needed for healthy plant development. Bacterial endophytes of Streptomyces sp. and Bacillus sp. have also been found to produce siderophores, as have *Pseudomonas fluorescens*, *Pseudomonas putida*, *Pantoea ananatis*, and *Pantoea agglomerans*. Citrus variegated chlorosis is caused by *Xylella fastidiosa*, which endophytic Methyl- obacterium species have been shown to inhibit by creating siderophores. Sunchoke plant development was considerably enhanced by the generation of siderophores by fungus. Moreover, recombinant *Trichoderma harzianum* endophytic strains colonising beans are described as producing siderophores (P. vulgaris). *Piriformospora indica*, an endophytic fungus, has been implicated in iron scavenging by generating siderophores (Bajaj et al., 2018). In particular, Epichlo festucae's siderophore synthesis was recognised to affect electrolyte balance and its mutualistic relationship with rye grass (Johnson et al., 2013)

5.4. Biological control agents

The exploitation of endophytic fungi as biological control agents (BCA) of phytopathogens, as that group of fungi, shows colonizing behaviour inside the plant. This plant pest has been found among different crops and can protect plants against various soil-native pathogens, such as *Aspergillus fumigatus, Botrytis cinerea, Blumeria graminis, Fusarium culmorum, F. oxysporum, Globisporangium ultimatum, Monilinia laxa, Moniliophthora perniciosa, Penicillium expansum*, *Phytophthora sp*., *P. palmivora, Plasmopara viticola, Puccinia polygoni-amphibii, Sclerotinia sclerotiorum* (Asai et al. 2013; Xu et al. 2013; Akay et al. 2014; Xiao et al. 2014; Zhang et al. 2014a, b; Zhou et al. 2014a, Arnold and Herre 2003; Waller et al. 2005; Kim et al. 2007; Chen et al. 2010; Hanada et al. 2010; Kurose et al. 2012; Zhang et al. 2014c). The potential use of microorganisms as biological control programmes to control pests or disease vectors such as *Metarhizium anisopliae* and *Beauveria bassiana*. The adverse utilization of antagonistic endophytes as biocontrol agents represents certain options for the management of some plant diseases, which minimalize the impact on the environment. Some endophytic fungi species used as biocontrol agents as Colletotrichum, Cladosporium, Fusarium, Pestalotiopsis and Trichoderma. Mechanisms of biocontrol include cell wall degrading enzymes, competition for nutrients, antibiosis, mycoparasitisms, inducing defense mechanisms and production of lytic enzymes (Zhang et al. 2014c). With the regular research, the efforts being for commercialization of endophytes as biocontrol agents, biomass production with the help of screening, in vivo and invitro testing which may lead to the sustainable development of agricultural resources.

5.5. Bioremediation/Biotransformation

Biodegradation is transforming pollutants from the surrounding environment with the help of biochemical processes/ biological actions of living organisms. Fungi have the potential to cope with this problem, through the breakdown of complex compounds and biosorption of heavy metals (Xiao et al., 2010). In the current scenario, the utilization of endophytic fungi to clean up the ecological system by degrading toxic pollutants such as hydrocarbons, polychlorinated biphenyls (PCBs), polyaromatic hydrocarbons (PAHs), radionuclides and metals. Fungi are well known for the production of extracellular enzymes and organic compounds such as cellulose, pectin, lignin, lignocelluloses, chitin and starch and anthropogenic substances such as hydrocarbons, pesticides and other xenobiotics. Several studies have attentive on white rot fungi like Phaenerochate chrysosporium degraded hydrocarbons, xenobiotics, pesticides and metals (Gadd 2007; Harvey and Thursten 2009). In a recent study, biodegradation of plastic through fungal strain helps to release plastic degrading enzymes which help to solve serious issues of pollution, the isolation of the endophytic fungi from native plants such as Psychotria flavida and Humboldtia brunoise which produce laccase enzymes and grew above the hydrophobic surface of plastic films. Endophytic fungi found novel and important sources of degradation of polycyclic aromatic hydrocarbons (PAHs). Recently, (Russel et al. 2011) reported that endophytic fungi can degrade synthetic polymer polyester polyurethane (PUR) by producing serine hydrolysis. Benzo(a)pyrene (BAP) degraded by endophytic Fusarium sp. isolated from the leaves of Pterocarpus macrocarpus Kurz (Juhasz and Naidu 2000). Degradation of phenanthrene by endophytic Phomopsis sp. of the rice plant, reported by, Tian et al. (2007). Ligninolytic enzymes were produced from the endophytic Xylariaceae strains isolated from the native place of the Thailand plant (Urairaj et al. 2003).

5.6. Catalyst Production

Endophytic fungi have a vital role in carbon and nitrogen cycling for the bioconversion of organic compounds through the enzymatic and non-enzymatic systems. Catalysts are important biological events which are widely utilized in agriculture, and industrial purpose (Suryanarayanan et al. 2012). Fungal endophyte is an essential source for the production of an enzyme which can produce various extracellular enzymes such as cellulase, amylase, chitinase, pectinase, and other catabolites (Jordaan et al. 2009; Borges et al. 2009; Rajulu et al. 2O11; Bezerra et al 2012). Cellulose is one of the major components of the plant cell walls that can be used by fungi as an energy source (Klemm et al. 2005). Cellulase is an enzyme that breaks down cellulose into simple sugars. Chitinolytic enzymes acquire importance in biotechnological applications. As chitinase is an enzyme that degrades the cell wall of pathogens, which is utilized in agricultural fields to control phytopathogens. Phosphomonoesters or phosphatases are hydrolytic enzymes which cleave the ester bond between the phosphate group and remove a phosphate group from a protein, some enzymes were found in endophytic fungi *Colletotrichum musae* and *Neotyphodium* species. Several endophytic fungi are well known for the production of lignocellulolytic enzymes

(Suryanarayanan et al. 2009), lignin is a diverse and uneven arrangement of phenyl propanoic polymer which helps to protect cellulose from enzymatic degradation, fungi produce extracellular enzymes which degrades the bond between a and b-carbons of the alkyl chain in lignin (Karsten 2008). Some endophytic fungi, such as laccase and peroxidase determined to direct the decomposition of lignin (Dai et al. 2010). The study reported that lignocellulosic material decomposed by fungal enzymes by two different methods (a) by the hydrolytic system such as xylanases and cellulases (b) by some ligninolytic enzymes such as laccases, ligninases and peroxidases (Correa et al. 2014). The research leads to the identification of enzymes modified in biotechnological applications and novel sources of the research field. Endophytic fungi are also known for the production of amylases which produce amylolytic enzymes (a-amylase, b-amylases and glucoamylases) which convert the starch into different simple sugar. Strong amylolytic action under in vivo conditions by endophytic *Fusicoccum sp.* (Champreda et al. 2007). In a further study, glucoamylase is extensively used in production. Such as Aspergillus sp. and Rhizopus sp. Source of production of glucoamylase (Pandey et al. 2000).

6. Conclusion:

Endophytic fungi have shown to be a viable source of natural compounds with a wide range of chemical compositions that is mostly unexplored. Research for bioactive substances from natural sources is vitally important that can be used to treat a variety of diseases in current circumstances. Endophytic fungi isolated from plants have drawn the attention of several researchers in both basic and clinical disciplines. As endophytic fungi provide great platforms for using bioactive chemical production via a biological pathway. Endophytic fungi isolated from medicinal plants produce a vast range of bioactive byproducts like alkaloids, peptides, flavonoids, phenolics, taxol, camptothecin, and others. With the use of contemporary biotechnology, including genetic engineering, metabolic engineering, and microbial fermentation, we are able to comprehend and regulate this crucial microorganism resources in order to increase its value to humanity. Further studies should be carried out in order to explore their theoretical study and their potential uses.

Table 1: Applications of endophytic fungi

Endophytic Fungi	Chemical Compound	Biological Events	Reference
Taxus andreanae	Diterpinoid	Anticancer	Strobel et al. 1997
Fusarium solani	Indole alkaloids	Antifungal	Abo-Kadoum et al. 2013
Alternaria sp.	Tenuazonicacid, monomethyl ether	Cytotoxic	Qin et al. 2009
Mycelia sterilia	Vincristine	Anticancer	Yang et al. 1994
Penicilliitm raistrick	Benzomalvin C	Antimalarial	Stierle et al. 2000
Xylaria sp.	7-Amino-4-methylcoumarin	antimicrobial	Liu et al. 2008
Pestalotiopsis microspora	1,3-dihydroisobenzofurans	antioxidant	Harper et al. 2013
Phomopsis sp.	Phomoxanthone A & B	Antimycobacterial Drug	Isaka et al. 2001
Pestalotiopsis guepinii	Phomopsidin & Phomopsichalasin	Antimalarial	Phongpaichit et al. 2007
Gliocladium roseum	2,6-dimethyl,3,3,5-trimethylcyclohexene,4-methyldecane, 3,3,6-trimethyl and undecane,4,4-dimethyl(Volatile hydrocarbons)	Biofuel	Maskey et al. 2003
Streptomyces. ochraceus and S. bottropensis	Trioxacarcins	Antitumorand antimalarial	Maskey et al. 2003
Trichophyton rubrum	Herbarin A	Antifungal	Gu 2009

Fusariumculmorum SVJM072	Taxol	Anticancer	Sonaimuthu et al. 2010
Chaetomium sp.	Cochliodinol, isocochliodinol	Cytotoxic activity	Debbab et al. 2009
Penicillium sp.	Meleargine and Chrysogine	Anticancer/ Antibacterial	Yunianto et al. 2014
Streptomyces sp.	Bonactin	Antibacterial	Schumacher et al. 2003
Teucrium sp.	Phenolic, flavonoid	Antimicrobial	Stanković et al. 2012
Penicillium aurantiogriseum	Indole alkaloids	Antimicrobial and antitumor activities	Abo-Kadoum et al. 2013
Trichoderma viride	Limonene and guaiol	Antimicrobial	Awad et al. 2018
Tubercularia sp.	Tuberculariols	Anticancer	Xu et al.2009
Pestalotiopsis sp.	Flavonoids	Antifungal	Ammar et al.2013
Aspergillus sydowii	Sydoxanthone A,B	Immunosuppresive	Song et al.2013
Mycelia sterilia	Vincristine	Anticancer	Kildgaard et al. 2014
Tricoderma sp.	Gliotoxin	Antimalarial, immune system suppressor	Pahl et al.1996
Emericellopsis sp.	Nortriterpenoid	Antibacterial	Harper et al.2003
Pestalotiopsis microspora	1,3-dihydroisobenzofurans	Antioxidant	Harper et al.2003

References:

1. Rana, K. L., Kour, D., Kaur, T., Devi, R., Negi, C., Yadav, A. N., ... & Saxena, A. K. (2020). Endophytic fungi from medicinal plants: biodiversity and biotechnological applications. In *Microbial endophytes* (pp. 273-305). Woodhead Publishing.

2. Gouda, S., Das, G., Sen, S. K., Shin, H. S., & Patra, J. K. (2016). Endophytes: a treasure house of bioactive compounds of medicinal importance. *Frontiers in microbiology*, *7*, 1538.

3. Roopa, G., Madhusudhan, M., Nischita, R., & Geetha, N. (2022). In vitro studies on anti-diabetic, anti-bacterial and phytochemical activities of endophytic fungal extracts from Salacia species. *J. Med. Plants*, *10*, 31-37.

4. Zheng, Y. K., Qiao, X. G., Miao, C. P., Liu, K., Chen, Y. W., Xu, L. H., & Zhao, L. X. (2016). Diversity, distribution and biotechnological potential of endophytic fungi. *Annals of Microbiology*, *66*, 529-542.

5. Paramanantham, P., Pattnaik, S., & Siddhardha, B. (2019). Natural products from endophytic fungi: synthesis and applications. *Advances in Endophytic Fungal Research: Present Status and Future Challenges*, 83-103.

6. Kumar, S., Aharwal, R. P., Shukla, H., Rajak, R. C., & Sandhu, S. S. (2014). Endophytic fungi: as a source of antimicrobials bioactive compounds. World J Pharm Pharm Sci, 3(2), 1179-1197.

7. Toghueo, R. M. K., & Boyom, F. F. (2020). Endophytic Penicillium species and their agricultural, biotechnological, and pharmaceutical applications. *3 Biotech*, *10*(3), 107.

8. Deshmukh, S. K. (2018). Translating endophytic fungal research towards pharmaceutical applications. *Kavaka*, *50*, 1-13.

9. Fouda, A. H., Hassan, S. E. D., Eid, A. M., & Ewais, E. E. D. (2015). Biotechnological applications of fungal endophytes associated with medicinal plant Asclepias sinaica (Bioss.). *Annals of Agricultural Sciences*, *60*(1), 95-104.

10. Choudhary, M., Gupta, S., Dhar, M. K., & Kaul, S. (2021). Endophytic fungi-mediated biocatalysis and biotransformations paving the way toward green chemistry. *Frontiers in Bioengineering and Biotechnology*, *9*, 664705.

11. Kumar, S., Aharwal, R. P., Shukla, H., Rajak, R. C., & Sandhu, S. S. (2014). Endophytic fungi: as a source of antimicrobials bioactive compounds. *World J Pharm Pharm Sci*, *3*(2), 1179-1197.

12. De Silva, N. I., Brooks, S., Lumyong, S., & Hyde, K. D. (2019). Use of endophytes as biocontrol agents. *Fungal Biology Reviews*, *33*(2), 133-148.

13. Mejía, L. C., Rojas, E. I., Maynard, Z., Van Bael, S., Arnold, A. E., Hebbar, P., ... & Herre, E. A. (2008). Endophytic fungi as biocontrol agents of Theobroma cacao pathogens. *Biological control*, *46*(1), 4-14.

14. Bilal, L., Asaf, S., Hamayun, M., Gul, H., Iqbal, A., Ullah, I., ... & Hussain, A. (2018). Plant growth promoting endophytic fungi Asprgillus fumigatus TS1 and Fusarium proliferatum BRL1 produce gibberellins and regulates plant endogenous hormones. *Symbiosis*, *76*, 117-127.

15. Wang, Y., & Dai, C. C. (2011). Endophytes: a potential resource for biosynthesis, biotransformation, and biodegradation. *Annals of Microbiology*, *61*(2), 207-215.

16. Krishnamurthy, Y. L., & Naik, B. S. (2017). Endophytic fungi bioremediation. *Endophytes: Crop Productivity and Protection: Volume 2*, 47-60.

17. Rana, K. L., Kour, D., Sheikh, I., Dhiman, A., Yadav, N., Yadav, A. N., ... & Saxena, A. K. (2019). Endophytic fungi: biodiversity, ecological significance, and potential industrial applications. *Recent advancement in white biotechnology through fungi: volume 1: diversity and enzymes perspectives*, 1-62.

18. Borges, W. D. S., Borges, K. B., Bonato, P. S., Said, S., & Pupo, M. T. (2009). Endophytic fungi: natural products, enzymes and biotransformation reactions. *Current Organic Chemistry*, *13*(12), 1137-1163.

19. Hridoy, M., Gorapi, M. Z. H., Noor, S., Chowdhury, N. S., Rahman, M. M., Muscari, I., ... & Mazid, M. A. (2022). Putative anticancer compounds from plant-derived endophytic fungi: a review. *Molecules*, *27*(1), 296.

20. Chandra, S. (2012). Endophytic fungi: novel sources of anticancer lead molecules. Applied microbiology and biotechnology, 95, 47-59.

21. Keglevich, P., Hazai, L., Kalaus, G., & Szántay, C. (2012). Modifications on the basic skeletons of vinblastine and vincristine. Molecules, 17(5), 5893-5914.

22. Kumar, S., Aharwal, R. P., Jain, R., & Sandhu, S. S. (2021). Bioactive molecules of endophytic fungi and their potential in anticancer drug development. Current Pharmacology Reports, 7, 27-41.

23. Rana, K. L., Kour, D., Sheikh, I., Yadav, N., Yadav, A. N., Kumar, V., ... & Saxena, A. K. (2019). Biodiversity of endophytic fungi from diverse niches and their biotechnological applications. *Advances in endophytic fungal research: present status and future challenges*, 105-144.

24. Manganyi, M. C., & Ateba, C. N. (2020). Untapped potentials of endophytic fungi: A review of novel bioactive compounds with biological applications. Microorganisms, 8(12), 1934.

25. Nasri, H., & Rafieian-Kopaei, M. (2013). Oxidative stress and aging prevention. International journal of preventive medicine, 1(1), 1101-1102.

26. Strobel, G., Ford, E., Worapong, J., Harper, J. K., Arif, A. M., Grant, D. M., ... & Chau, R. M. W. (2002). Isopestacin, an isobenzofuranone from Pestalotiopsis microspora, possessing antifungal and antioxidant activities. Phytochemistry, 60(2), 179-183.

27. Agrawal, S., Samanta, S., & Deshmukh, S. K. (2022). The antidiabetic potential of endophytic fungi: Future prospects as therapeutic agents. Biotechnology and Applied Biochemistry, 69(3), 1159-1165.

28. Baron, N. C., & Rigobelo, E. C. (2022). Endophytic fungi: A tool for plant growth promotion and sustainable agriculture. Mycology, 13(1), 39-55.

29. Burragoni, S. G., & Jeon, J. (2021). Applications of endophytic microbes in agriculture, biotechnology, medicine, and beyond. Microbiological Research, 245, 126691.

30. Nisa, H., Kamili, A. N., Nawchoo, I. A., Shafi, S., Shameem, N., & Bandh, S. A. (2015). Fungal endophytes as a prolific source of phytochemicals and other bioactive natural products: a review. Microbial pathogenesis, 82, 50-59.

31. Strobel, Gary, and Bryn Daisy. "Bioprospecting for microbial endophytes and their natural products." *Microbiology and molecular biology reviews* 67, no. 4 (2003): 491-502.

32. Strobel, Gary A. "Endophytes as sources of bioactive products." *Microbes and infection* 5, no. 6 (2003): 535-544.

33. Aly, Amal H., Abdessamad Debbab, Julia Kjer, and Peter Proksch. "Fungal endophytes from higher plants: a prolific source of phytochemicals and other bioactive natural products." *Fungal diversity* 41 (2010): 1-16.

34. Raimi, Adekunle, and Rasheed Adeleke. "Bioprospecting of endophytic microorganisms for bioactive compounds of therapeutic importance." *Archives of Microbiology* 203, no. 5 (2021): 1917-1942.

35. Berde, Chanda V. Parulekar, Prachiti P. Rawool, Pallaval Veera Bramhachari, and Vikrant B. Berde. "Endophytic Microbes from Medicinal Plants and Their Secondary Metabolites." *Plant Microbiomes for Sustainable Agriculture* 25 (2020): 97.

36. Strobel, Gary A., W. M. Hess, Jia-Yao Li, Eugene Ford, Joe Sears, Rajinder S. Sidhu, and Brett Summerell. "Pestalotiopsis guepinii, a taxol-producing endophyte of the Wollemi pine, Wollemia nobilis." *Australian Journal of Botany* 45, no. 6 (1997): 1073-1082.

37. Abo-Kadoum, M., Abo-Dahab, N., Awad, M., Abdel-Hadi, A., 2013. Marine-derived fungus, Penicillium aurantiogriseum AUMC 9757: a producer of bioactive secondary metabolites. J. Basic Appl. Mycol. 4, 77–83.

38. Qin, J.-C., Zhang, Y.-M., Hu, L., Ma, Y.-T., Gao, J.-M., 2009. Cytotoxic metabolites produced by Alternaria no. 28, an endophytic fungus isolated from Ginkgo biloba. Nat. Prod. Commun. 4, 1473–1476.

39. Yang X, Strobel GA, Stierle A , Hess WH, Lee J, et al. (1994) A fungal endophyte-tree relationship: Phoma sp. in Taxus wallachiana. Plant Sci 102: 1-9.

40. Stierle, A.A., Stierle, D.B., 2000. Bioactive compounds from four endophytic Penicillium sp. of a Northwest Pacific yew tree. In: Atta ur, R. (Ed.), Studies in Natural Products Chemistry. vol. 24. Elsevier, pp. 933–977.

41. Liu, X., Dong, M., Chen, X., Jiang, M., Lv, X., Zhou, J., 2008. Antimicrobial activity of an endophytic Xylaria sp. YX-28 and identification of its antimicrobial compound 7-amino-4-methylcoumarin. Appl. Microbiol. Biotechnol. 78, 241–247.

42. Harper JK, Arif AM, Eugene JF, Strobel GA, Porco Jr. JA, et al. (2003) Pestacin: a 1,3-dihydro isobenzofuran from Pestalotiopsis microspora possessing antioxidant and antimycotic activities. Tetrahedron 59: 2471-2476.

43. Isaka M, Jaturapat A, Rukseree K, Danwisetkanjana K, Tanticharoen M, et al. (2001) Phomoxanthones A and B, novel xanthone dimers from the endophytic fungus Phomopsis species. J Nat Prod 64: 1015-1018.

44. Phongpaichit S, Nikom J, Rungjindamai N, Sakayaroj J, Hutadilok-Towatana N, et al. (2007) Biological activities of extracts from endophytic fungi isolated from Garcinia plants. FEMS Immunol Med Microbiol 51: 517-525.

45. Strobel GA, Knighton B, Kluck K, Ren Y, Livinghouse T, et al. (2008) The production of myco-diesel hydrocarbons and their derivatives by the endophytic fungus Gliocladium roseum (NRRL 50072). Microbiology 154: 3319-3328.

46. Maskey, R.P., Helmke, E., Laatsch, H., 2003. Himalomycin A and B: isolation and structure elucidation of new fridamycin type antibiotics from a marine Streptomyces isolate. J. Antibiot. 56, 942–949.

47. Gu, W., 2009. Bioactive metabolites from Alternaria brassicicola ML-P08, an endophytic fungus residing in Malus halliana. World J. Microbiol. Biotechnol. 25, 1677.

48. Sonaimuthu V, Krishnamoorthy S, Johnpaul M (2010) Taxol producing endophytic fungus Fusarium culmorum SV JM072 from Medicinal plant of Tinospora cordifolia. J Biotechnol 150: S571-S576

49. Debbab A, Aly AH, Edrada-Ebel RA (2009) Bioactive secondary metabolites from the endophytic fungus Chaetomium sp. isolated from Salvia officinalis growing in Morocco. Biotechnol Agron Soc Environ13:229-234.

50. Yunianto P, Rusman Y, Saepudin E, Suwarso WP, Sumaryano W (2014) Alkaloid (meleaine and chrysogine) from endophytic fungi (Penicillium sp.) of L. Pak J Biol Sci 17: 667 -674.

51. Schumacher, R.W., Talmage, S.C., Miller, S.A., Sarris, K.E., Davidson, B.S., Goldberg, A., 2003. Isolation and structure determination of an antimicrobial ester from a marine sediment-derived bacterium. J. Nat. Prod. 66, 1291–1293.

52. Stanković, M., Stefanović, O., Čomić, L., Topuzović, M., Radojević, I., Solujić, S., 2012. Antimicrobial activity, total phenolic content and flavonoid concentrations of Teucrium species. OpenLife Sci. 7, 664–671.

53. Abo-Kadoum, M., Abo-Dahab, N., Awad, M., Abdel-Hadi, A., 2013. Marine-derived fungus, Penicillium aurantiogriseum AUMC 9757: a producer of bioactive secondary metabolites. J. Basic Appl. Mycol. 4, 77–83.

54.Panigrahy SK, Bhatt R, Kumar A (2021) Targeting type II diabetes with plant terpenes: The new and promising antidiabetic therapeutics. Biologia 76, 241-254.

55.Panigrahy SK, Jha A, Bhatt R, Kumar A (2020) Molecular docking and ADMET -based mining of terpenoids against targets of type -II diabetes. *Netw Model Anal Health Inform Bioinforma* 9.

56. Panigrahy SK, Bhatt R, Kumar A (2018): Hedychium coronarium Rhizomes: Promising Antidiabetic and Natural Inhibitor of α-Amylase and αGlucosidase, Journal of Dietary Supplements.

57. Panigrahy SK, Bhatt R, Kumar A (2020) Hedychium coronarium Rhizomes: Promising Antidiabetic and Natural Inhibitor of n-Amylase and n-Glucosidase. J Diet Suppl 17, 81-87.

58. Panigrahy SK, Bhatt R, Kumar A (2016): Reactive oxygen species: Sources, consequences and targeted therapy in Type-II Diabetes, Journal of Drug Targeting

59. Pahl, H.L., Krauss, B., Schulze-Osthoff, K., Decker, T., Traenckner, E.B.-m., Vogt, M., et al., 1996. The immunosuppressive fungal metabolite gliotoxin specifically inhibits transcription factor NF-kappaB. J. Exp. Med. 183, 1829–1840.

60. Harper J. K, Arif. AM, Ford E. J (2003) Pestacin: a 1, 3- dihydroisobenzofuranfrom Pestalotiopsis microspora possessing antioxidant and antimycotic activities. Tetrahedron 59: 2471–2476.

61. Kildgaard, S., Mansson, M., Dosen, I., Klitgaard, A., Frisvad, J., Larsen, T., et al., 2014. Accurate dereplication of bioactive secondary metabolites from marine-derived fungi by UHPLC-DAD-QTOFMS and a MS/HRMS library. Mar. Drugs 12, 3681–3705.

62. Ammar, M.I., Nenaah, G.E., Mohamed, A.H.H., 2013. Antifungal activity of prenylated flavonoids isolated from Tephrosia apollinea L. against four phytopathogenic fungi. Crop Prot. 49, 21–25.

63. Awad, N.E., Kassem, H.A., Hamed, M.A., El-Feky, A.M., Elnaggar, M.A., Mahmoud, K., et al., 2018. Isolation and characterization of the bioactive metabolites from the soil derived fungus Trichoderma viride. Mycology 9, 70–80.

64. Xu, R., Wang, M.Z., Lu, C.H., Zheng, Z.H., Shen, Y.M., 2009. Tuberculariols A–C, new Sesquiterpenes from the mutant strain M-741 of Tubercularia sp. TF5. Helv. Chim. Acta 92, 1514–1519.

65. Song XQ, Zhang X, Han QJ, Li XB, Li G, et al. (2013) Xanthone derivatives from Aspergillus sydavii, an endophytic fungus from the liverwort Scapania cilita S. lac and their immunosuppressive activities . Phytochem lett 6: 318- 321.