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Fungal endophytes: A potent biocontrol agent and a bioactive metabolites reservoir

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ABSTRACT

Endophytes protect the host plant for their entire life cycle and they have the ability to act as a biocontrol agent. Organisms protect the host plant through antibiosis, parasitism and competition mechanism in the biocontrol process. The improper and excessive use of agrochemicals makes the phytopathogens insensitive and leads to the development of resistant fungal pathogens. Chemical fungicides are expensive and have many negative impacts on the environment. The use of endophyte as the biocontrol agent is effective in controlling the plant disease and to achieve sustainable agriculture. Endophytes have antagonistic activity against disease-causing phytopathogens and also capable to produce antimicrobial, insecticidal, antioxidant, anti-tumor and anti-viral metabolites. Perfumoid, phomoenamide, joxysporidinone, alantrypinene, alantryleunone, (−)-4,6′-anhydrooxysporidinone and (−)-6-deoxyoxysporidinone are the few alkaloid compounds of endophytic fungi. Nidurufin, sterigmatocystin, averantin, 11a-methoxycurvularin 4, 11b-methoxycurvularin, tenellone H, phomopene and 1-chloro-2,4-dihydroxy-5-methoxy-7-methylanthraquinone are the endophytic fungal compounds reported with cytotoxic activity in the year between 2008-2019. The present review concentrates on the antagonistic activity of endophytes towards phytopathogens and their bioactive secondary metabolites with pharmacological properties.

1. Introduction

The use of medicinal plants leads to the detection and advancement of modernized therapeutics to treat different varieties of ailments and they are the potential source for natural products (Venieraki et al., 2017). Plants are considered to be the “bio-factories” by pharmaceutical biology in generating potent compounds with therapeutic values (Baker and Satish, 2012). The co-existence of diverse microbes with the plant can rise to both the benefit and plague. As the inter organismal interaction continues, it results in the intense condition of the symbiotic and parasitic association (Baker and Satish, 2012). All over the world, the medicinal plant's usage has rapidly increased due to the rising need for secondary metabolites, herbal drugs and natural health products. From 1981 to 2014, natural products based small molecule drugs were approved more than 51% (Venieraki et al., 2017). For thousands of years, natural products such as metabolites and by-products of plants, animal and microbes are overworked to be used for human needs. The compounds used for medicine are mainly derived from the plant source. When the endophyte lives in association with the plant, discernible harm is not found in both the interacting partners and the benefit is always based on the endophyte and host (Kamana et al., 2016). Natural products with antimicrobial activities can be used directly or by inducing the resistance to plants as the biological control agent to reduce the adverse effects of pesticides while controlling the plant's disease (Stangarlin et al., 2011). Phytopathogens are restricted by the use of plant extracts mainly collected from tree species that includes neem, eucalyptus and ocimum, camphor, yarrow, ginger, mint, rue, garlic, citronella of herbaceous species (Stangarlin et al., 2011). Recent studies reported the production of novel antimycotics, antibiotics, immunosuppressant, antineoplastic compounds and topoisomerase inhibitors from the novel endophytes. In the microbial plant symbionts, fungal endophytes are a comparatively less studied group (Verma et al., 2008).

2. Endophytic fungi

In 1866 De Bary was the first to propose the concept “Endophytes” (Liu et al., 2018). Endophytic fungi and/or bacteria were found to live within the tissue of almost all vascular plant species and they are found in all the host plant organs and even their seeds are found to harbor endophytes (Venieraki et al., 2017). Medicinal plants are recognized as the storehouse of endophytes which can synthesis novel pharmaceutically important secondary metabolites (Elgorban et al., 2018). The health condition and agronomic characters of the plants are affected by

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the harmonious relationship between host plants and their profitable endophytes (Liu et al., 2018). Approximately 5% of fungal species have been described which is a small fraction of over all million fungal species estimated on earth. The biochemistry, physiology, distribution and ecology of the host plant can be influenced by the endophytes and the survival of endophytes acknowledged from the past one hundred years (Laxmipriya Padhi and Kishore Mohanta, 2013). Passenger endophytes, obligate endophytes and facultative endophytes are three groups of endophytic community classified. The endophytes which live in association with the host plant and can also be found in other habitats are referred to as facultative endophytes. Obligate endophytes is the one which found in the inner tissue of the host but they are not able to colonize another habitat. In the absence of competition and plant protection, passenger endophytes can randomly penetrate the plant tissue (Brum et al., 2012). Geographic location, season and tissue type are the factors influences the species composition, diversity of species and colonization frequency of fungal endophytes community (Yao et al., 2017). In plants and lichen, the number of endophytic fungi are estimated to be 1 million species based on the recent reports on the ubiquitousness of fungi. Sea grasses, palms and large trees are the diverse groups of plants and lichens used to isolate endophytes nowadays (Laxmipriya Padhi and Kishore Mohanta, 2013). Asthma, mental stress and blood stasis are treated with the *Tricyrtis maculate*, the healthy leaves of this medicinal plant which harbors an endophyte *Phomas bellidis* (Dzoyem et al., 2017). Through the specific interaction between the fungal and the host medicinal plants, the endophytes have an effect on the quality and quantity of plant-derived crude drugs (Elgorban et al., 2018). Until the presence of a particular carbon source, the decomposition enzyme cannot be produced by the endophytes (Rajesh and Rai, 2013). By producing enzymes and bioactive metabolites, endophytic fungi directly struggle for nutrition and space with pathogens. The endophyte with multi-beneficial impact and commercial potential are used as an agent for the prosperous sustainable agriculture (Anisha et al., 2018).

The location and climatic conditions of the host plant has a great impact on the frequency and diversity of fungal endophyte population (Kouipou Toghueo and Boyom, 2019). *Clonostachys, Discula, Glomerella, Cylindrocarpon, Dendrodochium, Phomopsis, Apiognomonia, Colletotrichum, Chloroscypha Sirodothis, Gremmeniella, Diaporthe, Phialocephala, Cryptocline* are fungal genera of endophytes commonly reported being isolated from the foliage of woody perennials (Jeffrey K. et al., 2014). *Alternaria, Acremonium, Botryospharia, Cochlonema, Colletotrichum, Chaetomium* and *Diaporthe* are few fungal genera reported being present in the plants of *Terminalia* spp. (Kouipou Toghueo and Boyom, 2019). *Azadirachta Indica* was found to harbor endophytic fungi belonging to the genus of *Fusarium, Xylaria, Penicillium, Phoma, Pestalotiopsis, Nigrospora Alternaria, Periconia, Stenella* and *Cladosporium* (Chutulo and Chalannavar, 2018). The fungal endophytes in the genus of *Phyllosticta, Phoma, Colletotrichum* and *Phomopsis* have a wide range of host plants (Selim et al.,2012).

3. Endophytic fungal impact on plant protection

Endophytes are capable to stimulate and activate the stress response of the host plant firmly and promptly when compared with non-symbiotic plants. Some reports revealed the protection of host plant from drought conditions by their endophytes and increase the hosts tolerant for heat and salt (Jalgaonwala et al., 2011). Endophytic fungi act as biocontrol agents and also protects the host plant from infections for the entire life cycle of endophytes. These types of fungi easily adapt to the negative environmental conditions and also helps in host plant defense (Wu et al., 2018). When endophytes colonize inside the live host, their defense, tolerance against biotic and abiotic stresses and physiology are affected by in vitro production of secondary metabolites from endophytic fungi (Kusari et al., 2014). Induction of biotic or abiotic stress tolerance, germination and shoot growth promotion and production of secondary metabolites with bioactivities are the beneficial effects of endophytes for the host (Xie et al., 2018). By interacting with their host plant, endophytes are able to secure the plant from adverse effects and improve the plant growth, prevents from plant pathogens, increases the crop yield and also helps in phytoremediation (Xie et al., 2018). When the plant comes in contact with biotic or abiotic elicitor, the latent of plant defense systems are activated by the induction of resistance (Stangarlin et al., 2011). In the process of evolution and co-existence for the long term, neutralism, a continuum of mutualism and antagonism are the special interaction of the host plant and their fungus that establishes a diverse relationship between them (Jia et al., 2016). The occupation of endophytic ecology and endophytic fungi induce the production of phytoalexins which might be the major reason in the plant protection and antagonistic activity of fungal endophytes towards the pathogens (Gao et al., 2010). In the depository of bio pesticides, endophytes are the new addition as it posses impressive and promising novel methods for protecting plants (Nieuwesteeg, 2015). The study reported that the induction of *Aspergillus terreus* and *Penicillium citrinum* in the sunflower plants improved the overall biomass yield and also the sunflower plants displayed disease resistance towards the *Sclerotium rolfsii* (Zea and Devi, 2017). In agriculture, fungal endophyte is the significant biocontrol agent in controlling pest, insects, nematodes and various pathogenic microbes (Zea and Devi, 2017).

4. Diseases causing phytopathogens

The bacterial blight of pear tree was the first bacterial disease discovered by TJ Burril in 1839–1916. *Micrococcus amylovorus* which the pathogen name later changed to *Erwinia amylovora* is the one isolated from that bacterial diseased plant. The development of bacterial plant pathology has started to grow from his discovery. (Arwiyanto, 2019). Bacterial speck affects leaves and fruits of the tomato plant which reduces the value of specked fruits in the market (Damicone and Brandenberger, 2012). The wetness of leaf (55 F–77 F of cooler temperatures) is suitable for *Pseudomonas syringae* pv to cause the bacterial speck where the defoliation in the plant results in its lower yield (Damicone and Brandenberger, 2012). In the global food production, about 27–42% of food production loss takes place due to the crop losses that results from the plant pathogens caused plant disease. Unless the approach applied in the management of disease it would have been led to the double loss of food production (SINGH, 2014). Disease in plants are mostly caused by oomycetes and fungi and in animals and humans, acute or chronic are caused by fungal toxins (Silva et al., 2018). In the tomato plant, growth retardation, alteration of leaves and fruit color, death of the plant, decreased yield, stunting of plants are the symptoms of virus infections caused by alfalfa mosaic virus, tobacco mosaic virus, tomato spotted wilt, beet curly top virus and impatiens necrotic spot viruses. Insects are the major source of spreading the infection but in some cases, the exposure of infected sap with plant wounds may also be involved (Damicone and Brandenberger, 2012). The stimulation of systemic acquired resistance, induced systemic resistance and hypersensitive response in the plants are associated with its defense feedback (Baiyee et al., 2019).

Polyphenol oxidase, chitinase, β-1,3- Glucanase and peroxidase are enzymes involved in defense mechanism when the host plant comes in contact with the pathogens. The preceding chemical and physical barriers in the defense response involve in minimizing the infection and obstructing the establishment of pathogens (Baiyee et al., 2019). *Fusarium flocciferum, Fusarium solani, Fusarium oxysporum, Alternaria tenuissima, Alternaria panax, Cylindrocarpon destructans, Phytophthora cactorum, Phoma herbarium, Cylindrocarpon didymium* and *Rhizoctonia solani* are the root rot fungal pathogens which cause disastrous root-rot disease. The most destructive root-rot disease complex reduces the yield thereby, it leads to lowering the active ingredients content or no harvest (Zheng et al., 2017). The growth of the fungal species are suppressed by

Table 1
Antagonistic activity of fungal endophytes towards plant pathogens.

Endophytic fungi	Host plant	Phytopathogen	Reference
Trichoderma viride	*Spilanthes paniculata*	*Alternaria solani* *Colletotrichum capsici* *Fusarium solani* *Pythium aphanidermatum*	Talapatra et al. (2017)
Lasiodiplodia pseudotheobromae, *Fusarium* sp, *Xylariales* sp.	*Houttuynia cordata* Thumb.	*Fusarium oxysporum* *Sclerotium rolfsii* *Alternaria brassicicola*	Aramsirirujiwet et al. (2016)
Aspergillus flavipes	*Steviare baudiana* Bertoni	*Sclerotinia sclerotiorum*	Verma et al. (2014)
Penicillium spp.	*Musa* spp.	*Fusarium oxysporumFusarium* sp.	Ting et al. (2010)
Choiromyces aboriginum	*Phragmites australis*	*Rhizoctonia solani* *Sclerotium rolfsii* *Rhizoctonia cerealis* *Fusarium graminearum* *Fusarium oxysporum* f. sp. perniciosum *Fusarium oxysporum* f. sp. vasinfectum *Gaeumannomyces graminis* var. tritici	Cao et al. (2009)
Stachybotrys elegans	*Phragmites australis*	*Rhizoctonia cerealis* *Fusarium graminearum*	Cao et al. (2009)
Cylindrocarpon sp.	*Phragmites australis*	*Rhizoctonia solani* *Rhizoctonia cerealis*	Cao et al. (2009)
Colletotrichum gloeosporioides *Acaulospora terricola* *Bjerkandera adusta* *Diaporthe phaseolorum* *Diaporthe helianthi*	*Vitis labrusca* L.	*Fusarium oxysporum* f. sp herbemontis	Brum et al. (2012)
Penicillium simplicissimum *Leptosphaeria* sp.	Cotton Roots	*Verticillium dahliae*	Yuan et al. (2017)
Alternaria sp. *Diaporthe* sp. *Nigrospora oryzae*	*Olea europaea* L.	*Colletotrichum acutatum*	Landum et al. (2016)
Talaromyces funiculosus Rhexocercosporidium sp. *Fusarium solani*, *Fomitopsis* sp. *Purpureocillium lilacinum*	*Sophora tonkinensis* Gapnep	*Fusarium solani* *Colletotrichum gloeosporioides*	Yao et al. (2017)
Nigrospora sphaerica	*Cornus florida*	*Fusarium oxysporum* *Fusarium solani* *Macrophomina phaseolina*	Mt (2018)
Gliocladium catenulatum	*Theobroma cacao*	*Crinipellis perniciosa*	Rubini et al. (2005)
Trichoderma gamsii	*Panax notoginseng*	*Epicocum nigrum* *Scytalidium lignicola* *Pleospora herbarum* *Fusarium flocciferum*	Chen et al. (2016)
Trichoderma citrinoviride	*Panax ginseng*	*Rhizoctonia solani* *Botrytis cinerea* *Alternaria panax* *Cylindrocarpon destructans* *Phytophthora cactorum* Pythium spp. *Botrytis cinerea* *Cylindrocarpon destructans*	Park et al. (2018)
Cladosporium oxysporum *Pestalotiopsis uvicola* *Trichoderma koningiopsis* *Penicillium chrysogenum*	*Panax notoginseng*	*Alternaria panax* *Fusarium oxysporum* *Fusarium solani* *Phoma herbarum* *Mycocentrospora acerina*	Zheng et al. (2017)
Rhizopycnis vagum	*Zingiber officinale* Rosc.	*Rhizoctonia solani* *Corynespora cassiicola* *Colletotrichum acutatum* *Phytophthora infestans* *Fusarium oxysporum* *Sclerotium rolfsii*	Anisha et al. (2018)
Paenibacillus polymyxa	*Morinda citrifolia* L.	*Aspergillus aculeatus*	Liu et al. (2018)
Pestalotiopsis spp. *Curvularia* spp. *Fusarium* spp *Fusarium* spp. *Tolypocladium* spp. *Fusarium* spp.	*Theobroma cacao* (cacao)	*Phytophthora palmivora* (black-pod disease)	Roge'rio Eiji Hanada et al. (2010)
Pestalotiopsis spp.	*Theobroma grandiflorum* (cupuaçu)	*Phytophthora palmivora*	Rogério Eiji Hanada et al. (2010)
Muscodor yucatanensis	*Monarda citriodora*	*Sclerotinia* sp. *Colletotrichum capsici* *Aspergillus flavus* *Aspergillus fumigatus*	Katoch and Pull (2017)

(*continued on next page*)

Table 1 (*continued*)

Endophytic fungi	Host plant	Phytopathogen	Reference
Trichoderma asperellum	Lettuce leaves	*Corynespora cassiicola* *Curvularia aeria* (leaf spot fungi)	Baiyee et al. (2019)
Penicillium commune *Aspergillus oryzae*	*Monarda citriodora*	*Sclerotinia* sp.	Katoch and Pull (2017)
Epicoccum nigrum	Sugarcane	*Fusarium verticillioides* *Ceratocystis paradoxa*	Luiza and Sebastianes (2012)

hydrolyzing the chitin and β-1,3-glucan proteins of numerous fungal phytopathogens and chitinase (PR3) and β-1,3-glucanase (PR2) is pathogenesis-related (PR) proteins involved in this process (Baiyee et al., 2019).

5. Effect of phytopathogens on host plant

The term 'hosts' refers to the plants affected by a living organism that is pathogenic and it causes structural and physiological abnormalities in the diseased plants (Leonberger et al.). Bacteria, fungi, phytoplasmas, nematodes, parasitic seed plants, viruses and oomycetes (refers as water molds) are the organisms causing plant diseases. Development of symptoms like rots, cankers, wilt and leaf spots may take time. After the initial occurrence, the infection may take several days to even years for the development of the disease (Leonberger et al.). Alteration in temperature, transpiration rate, morphology and the release of volatile organic compounds from infected plants are different parameters used in identifying crop diseases indirectly. When a number of samples need to be analyzed in the high-throughput analysis, serological and molecular methods are the direct method used in the identification and detection of diseases in the plant (Fang and Ramasamy, 2015). Reproduction and nutrients at the investment of host plant are some of the utilization of plant pathogens. In the past, severe calamities are generated by the plant pathogens and this biotic constraint causes sustained threat in the production of food. The use of physical methods, agrochemicals, genetically engineered plants and the development of resistant plant by plant breeding are pathogens controlling methods with a few limitations (SINGH, 2014).

Resistant plant varieties are not opposing all the plant disease and it consumes lots of time to develop the plant by plant breeding. National governmental policies banned the genetically engineered resistance that is another sensitive issue. The usage of agrochemicals has a negative impact on human health, soil microfauna and soil fertility and its pricey (SINGH, 2014). Based on the infection period, environmental conditions, the resistance of host and aggressiveness of the pathogen, the disease severity may range from moderate symptoms to slump of the plant infected with the pathogen (Al-sadi, 2017). The symptoms of disease in the plant differs based on the part affected and pathogen involved in the infection. Wilt, fruit spots, fruit rots, leaf blights, leaf spots, dieback, root rots and deterioration are the disease symptoms (Al-sadi, 2017). Competitive ability and fitness of the host are lowered due to their sensitivity to pathogens, pests and the expenditure in defense mechanism (Creissen et al., 2016).

6. Antagonism of endophytic fungi

The control of microbes by the use of antagonistic organisms and the reduction of inoculums which determines the disease development are referred to as biological control (Stangarlin et al., 2011). Parasitic seed plants, nematodes, viruses, bacteria, oomycetes and fungi are the organisms involved in causing disease to the plants (Leonberger et al.). The production of compounds with antimicrobial activity is extensively studied and most easily identified mechanisms in the inhibition of pathogens. When the endophytes inhibit the pathogens, they involved in the nutrients and colonizing sites competition, host plant defense stimulation, antimicrobial compounds production with biocontrol activity that is identical to other soil-borne biocontrol agents (Ting et al., 2010). Phytopathogens are susceptible to single or multiple kinds of antibiotics produced by a group of biocontrol strains and the antibiotics includes polypeptides, aromatic, terpenoids and alkaloid compounds. 3,11,12-trihydroxycadalene is one among the five cadinane sesquiterpenes derivatives isolated from *Cassia spectabilis*, a fungal endophyte of *Phomopis cassia* and the compound showed strong antifungal activity towards *Cladosporiumclad sporioides* and *Cladosporium sphaerospermum* (Gao et al., 2010). All over the world market, the use of biopesticides from nature and biocontrol agents are expanding widely. Biopesticides are not used individually, rather than as part of an integrated pest management system. In the overall pesticide usage, biopesticides had 0.2% market share in the year of 2000 and in six years the share was elevated to 2.5% (Nieuwesteeg, 2015). The antagonistic effect of endophytic fungi against phytopathogens were analyzed by the dual culture *in-vitro* method and some of them are listed in Table:1

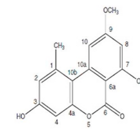
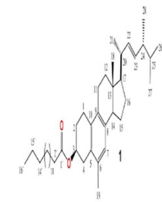
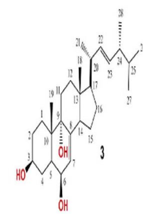
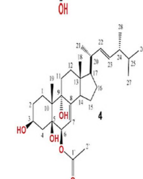
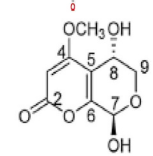
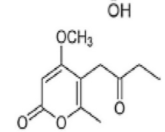
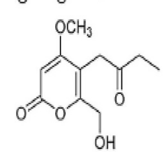
Nutrients and space competition, plant growth promotion and systemic resistance induction are the indirect and hyperparasitism, lytic enzymes and antibiotics production are the direct method of biological control agents to antagonize the pathogens (Mt, 2018). In the biocontrol process, organism directly involved in the mechanisms like parasitism, competition and antibiosis. Plant pathogens are controlled by lots of biological control mechanisms (Ownley et al., 2010). The defense mechanism of the host plant towards phytopathogens and pests are improved by high insecticidal compounds production of some of their endophytes (Katiski et al., 2018). The black-pod rot disease in the cacao can effectively be suppressed by the isolated fungal endophyte (Venkateswarulu et al., 2018). In the greenhouse conditions, macrophomina root rot and powdery mildew are controlled by the several potential bacterial endophytes associated with Cornus florida and phytophthora root rot are also controlled by some of the potent endophytes (Mt, 2018).

The endophytic strain G3 detached from *Triticum aestivum* L. stem showed a wide range of antifungal activity towards numerous phytopathogens that include *Valsa sordid, Cryphonectria parasitica, Rhizoctonia* cerealis and *Botrytis cinerea* in the *in-vitro* condition. G3 strain was identified to belong to the genus Serratia by sequencing 16S rDNA. A few endophytes have the ability to protect the plant against numerous pathogens (O'Brien, 2017). The wheat resistance for the tan spot and rust pathogens has increased by the fungus, C*haetomium globosum* (Kamana et al., 2016). In the endophytic and rhizosphere bacteria, the potent BCAs are actinomycetes and found in the Bacillus, Pseudomonas genera. The species in the Trichoderma genus are efficient as the biocontrol agent among the fungi (O'Brien, 2017). Bread wheat and diverse cereals affected by the ergot disease. In humans, ergotism is caused due to the consumption of bread made from the flour contaminated with the fungi of Claviceps genus. Hallucinations, peripheral sensation loss and death are the causes recorded for ergotism (Al-sadi, 2017).

7. Fungal endophyte as biocontrol agent

In 1914 C. F. Von was the first to use a biological agent in the management of plant disease. Pesticides and chemical fertilizers are the two different groups of agrochemicals. Phosphorus, potassium and nitrogen are the minerals included in chemical fertilizers. Fungicides,

Table 2
Secondary metabolites of endophytic fungi with pharmacological activity.

Fungal source	Host plant	Compound name	Structure	Activity against	References
Alternaria sp. Samif01	*Salvia miltiorrhiza Bunge*	Alternariol 9-methyl ether		The compound showed antimicrobial activity towards *Agrobacterium tumefaciens, Bacillus subtilis,* Ralstonia solanacearum, *Staphylococcus haemolyticus* and *Xanthomonas vesicatoria* with MIC of 75,50,75,37.5,75 μg/ml	Lou et al. (2016)
Fusarium sp.	*Mentha longifolia* L.	Fusaristerols B [(22*E*,24*R*)-3-palmitoyl-19 (10 → 6)-abeo-ergosta-5,7,9,22-tetraen-3β-ol] fusaristerols C [(22*E*,24*R*)-ergosta-7,22-diene-3*β*,6*β*,9*α*-triol]		LOX inhibitory potential with an IC50s of 3.61 μM	Khayat et al. (2019)
		Fusaristerols D [(22*E*,24*R*)-ergosta-7,22-		Antiinflammatory activity	
		Diene-3β,5α,6β,9*α*-tetraol 6-acetate]		Antiinflammatory activity	
Kadsura angustifoli	*Phomopsis asparagi*	Phomaspyrones C		The compound exhibited cytotoxicity against HL-60 and K562 cells	Song et al. (2017)
		Phomaspyrones D		Cytotoxic effect	
		Phomaspyrones E		Cytotoxic effect	

(*continued on next page*)

Table 2 (*continued*)

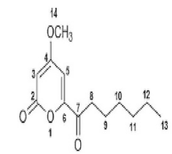
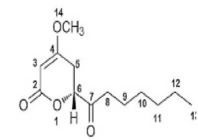
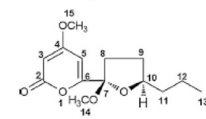
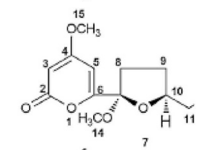
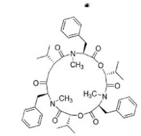
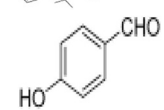
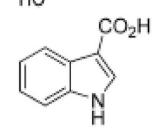
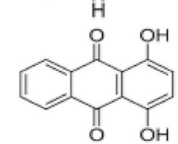
Fungal source	Host plant	Compound name	Structure	Activity against	References
Xylariales sp.	-	Xylariaopyrones A		Antimicrobial activity	Guo et al. (2018)
		Xylariaopyrones B		Antimicrobial activity	
		Xylariaopyrones C		Antimicrobial activity	
		Xylariaopyrones D		Antimicrobial activity	
Epicoccum nigrum	*Entada abyssinica*	Beauvericin		Antibacterial activity towards *Salmonella typhimurium* and *Bacillus cereus* with MIC values of 3.12 and 6.25 g/ml	Dzoyem et al. (2017)
		Parahydroxybenzaldehyde		Cytotoxic effect	
		Indole-3-carboxylic acid		Cytotoxic effect on both normal and tumor cells (Vero cells, THP-1 and RAW 264.7	
		Quinizarin		Cytotoxic effect	

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Table 2 (*continued*)

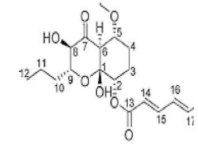
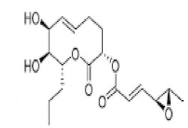
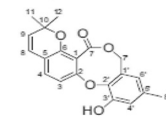
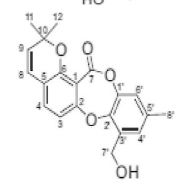
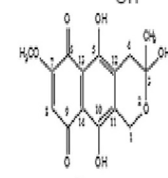
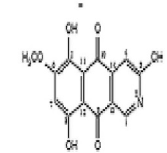
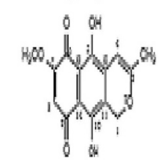
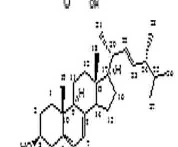
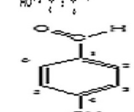
Fungal source	Host plant	Compound name	Structure	Activity against	References
Tricyrtis maculata	*Phoma bellidis*	Bellidisins A		Both the compounds showed cytotoxic effect towards adenocarcinomic human alveolar basal epithelial cells A549, human breast cancer cell line MCF-7, human colorectal adenocarcinoma cell line SW480 and human leukaemia cell line HL-60 reported in both the compounds	Wang et al. (2019)
		Bellidisins D			
Phellodendron amurense.	*Diaporthe* sp.	Diaporthols A		Diaporthols A and Diaporthols B reavealed anti-migration activity was found at a concentration of 20 lM in TGF-b1-elicited MDA-MB-231 (breast cancer cells)	Nakashima et al. (2018)
		Diaporthols B			
Cassia alata Linn.	*Fusarium solani*	Fusarubin		Antimicrobial activity against *Escherichia coli, Bacillus megaterium, Pseudomonas aeruginosa* and *Staphylococcus aureus*	Khan et al. (2018)
		Bostrycoidin		Antimicrobial activity	
		Anhydrofusarubin		The compound showed antioxidant activity with IC50 values of 12.4 μg/mL	
		Ergosterol		Ergosterol- no activity	
		4-hydroxybenzaldehyde		4-hydroxybenzaldehyde is active against *E.coli* and antioxidant activity with IC50 values of 28.9 μg/mL	

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Table 2 (*continued*)

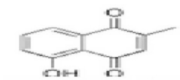
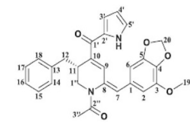
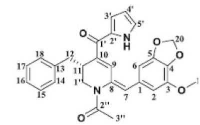
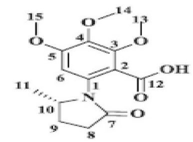
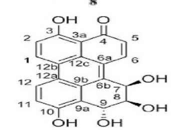
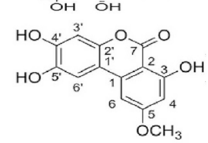
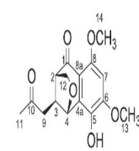
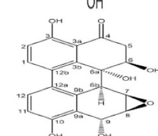
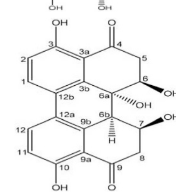
Fungal source	Host plant	Compound name	Structure	Activity against	References
Cladosporium cf. tenuissimum	*Terminalia pallida*	Plumbagin (5- hydroxyl- 2- methylnaptalene-1,4-dione)		Antimicrobial activity against *Fusarium moniliforme, Sitophilus oryzae, Candida albicans, Candida tropicalis* with the MIC of 12.5 mg/mL	Venkateswarulu et al. (2018)
Penicillium janthinellum	*Panax notoginseng*	Brasiliamide J-a		Brasiliamide J-a displayed significant inhibitory activities against *Bacillus subtilis and Staphylococcus aureus* with MIC values of 15 and 18 μg/ml, respectively	Xie et al. (2018)
		Brasiliamide J-b		Brasiliamide J-b exhibited inhibitory effect towards *Bacillus subtilis* MIC 35 μg/ml and *Staphylococcus aureus* MIC 39 μg/ml	
		Peniciolidone		Peniciolidone showed inhibitory activities against B. subtilis MIC 50 μg/ml and *S. aureus* (MIC 60 μg/ml)	
Alternaria sp.	*Broussonetia papyrifera*	Altertoxin IV		Antitumor activities	Zhang et al. (2016)
		3,4′,5′-trihydroxy-5-methoxy-6H-benzo [c]chromen-6-one (2)		Cytotoxic activities against tested cell lines, with IC50 values of 1.47, 2.11 and 7.34 μg/mL, respectively	
Fusarium sp.	Chinese agarwood	(2S,3 S,4 S)-8-Dehydroxy-8-methoxyl-dihydronaphthalenone		Acetylcholinesterase inhibitory activity with the inhibition ratio of 11.9% at the concentration of 50 μmol/ml	Xiao et al. (2018)
Alternaria sp.	*Pinus ponderosa*	3,6,6a,9,10-pentahydroxy-7,8-epoxy-4-oxo-4,5,6,6a,6b,7,8,9-octahydroperylene		Antileishmanial activity against *Leishmania donovani* with IC90 ¼ 8.28 mg/ml and IC50 ¼ 2.55 mg/ml	Tantry et al. (2018)
		3,6,6a,7,10-pentahydroxy-4,9-dioxo- 4,5,6,6a,6b,7,8,9-octahydroperylene		Antileishmanial activity against *Leishmania donovani* with IC90 ¼ 9.54 mg/ml and IC50 ¼ 4.40 mg/ml Antimalarial activity against both the chloroquine resistant (W2) clones and chloroquine sensitive (D6) of *P. falciparum* with IC50 ¼ 3.65 mg/ml and 4.24 mg/ml Cytotoxicity activity against VERO cells (mammalian kidney fibroblasts) with IC50 ¼ 3.59 mg/ml	

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Table 2 (*continued*)

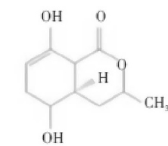
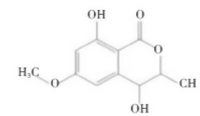
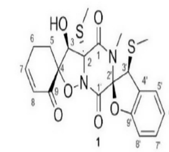
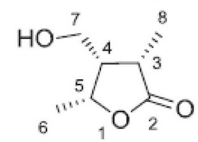
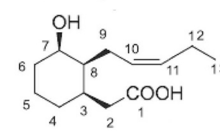
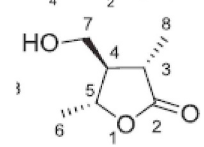
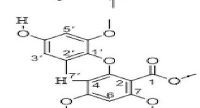
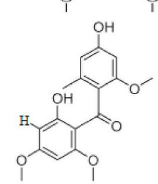
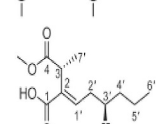
Fungal source	Host plant	Compound name	Structure	Activity against	References
Phoma sp.	*Cinnamomum mollissimum*	4-hydroxymellein		Inhibitory activity against *Bacillus subtilis* (97.3%) and P388 murine leukemic cells (94.6%)	Santiago et al. (2014)
		4,8-dihydroxy-6-methoxy-3- methyl-3,4-dihydro-1H-isochromen-1-one		Inhibitory activity against *Aspergillus niger* (56.1%) and P388 murine leukemic cells (48.8%)	
Botryosphaeria mamane	*Bixa orellana* L.	Botryosulfuranols A		Cytotoxic effect towards HepG2,HT-29,Caco-2 and HeLa (cancer cell line) and Vero, IEC6 (healthy cell line)	Barakat et al. (2019)
Lasiodiplodia pseudotheobromae	*Aegle marmelos*	Lasdiplactone		Inhibitory effect on xanthine oxidase with IC50 of 0.38 ± 0.13 µg/ml.	Kumar et al. (2018)
		Lasdiploic acid		IC50 of 0.41 ± 0.1 µg/ml was found in invitro xanthine oxidase assay.	
		–4– (Hydroxymethyl)–3,5–dimethyldihydrofuran–2 (3H)–one		Inhibitory effect on xanthine oxidase with IC50 of 0.35 ± 0.13 µg/ml	
Xylaria sp.	*Panax notoginseng*	Xylarianins A		The compound showed inhibitory activity towards human carboxylesterase 2 with IC50 values of 10.43 ± 0.51 µM	Zhang et al. (2018)
		5,9,11-trimethoxy-3,13-dihydroxy benzophenone		Inhibitory effect against human carboxylesterase 2 with IC50 values of18.86 ± 1.87 µM	
		2-hexylidene-3-methyl succinic acid 4-methyl ester		Inhibitory effect against human carboxylesterase 2 with IC50 values of 20.72 ± 1.51 µM	

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Table 2 (*continued*)

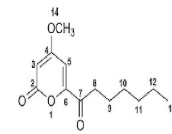
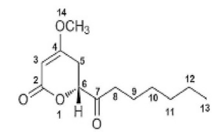
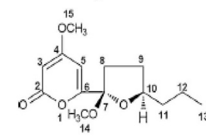
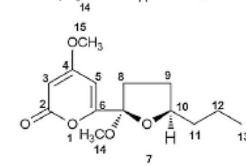
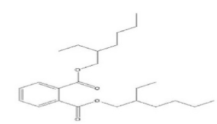
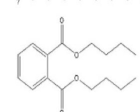
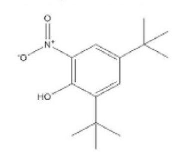
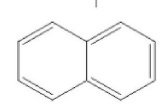
Fungal source	Host plant	Compound name	Structure	Activity against	References
Xylariales sp.	*Distylium chinense*	Xylariaopyrones A		Antimicrobial activity	Guo et al. (2018)
		Xylariaopyrones B		Antimicrobial activity	
		Xylariaopyrones C		Antimicrobial activity	
		Xylariaopyrones D		Antimicrobial activity	
Alternaria sp.	*Salvadora persica*	1,2-Benzenedicarboxylic acid, bis (2- ethyhexyl) ester		Antimicrobial activity	Elgorban et al. (2018)
		1-Octadecene		Anticancer, antimicrobial and antioxidant activity	
		1,2-Benzenedicarboxylic acid, dibutyl ester (CAS) Butyl phthalate		Antioxidant and antimicrobial activity	
		Phenol, 2,4-di-*t*-butyl-6-nitro		Antimicrobial and anticancer activity	
		Naphthalene		Insecticidal activity	

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Table 2 (*continued*)

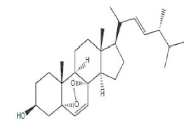
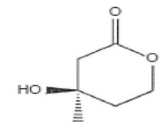
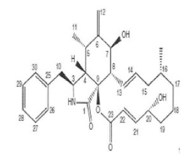
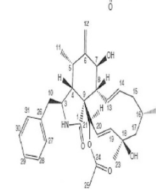
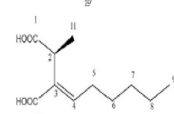
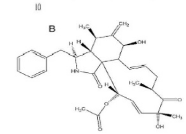
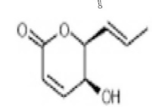
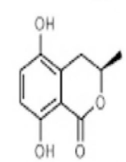
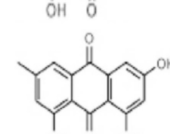
Fungal source	Host plant	Compound name	Structure	Activity against	References
Aspergillus sp.	*Bauhinia guianensis*	Ergosterol peroxide		Lethality of the compound against *Artemia salina* LC50 »250 µg/ml	Feitosa et al. (2016)
		Mevalonolactone		LC50 for *Artemia salina* is »250 µg/ml	
		Cytochalasin B		Lethality of the compound against *Artemia salina* LC50 is 24.9 µg/ml	
		Cytochalasin H		Lethality of the compound against *Artemia salina* LC50 69.1 is µg/ml	
Xylaria spp.	*Paullinia* cupana	Piliformic acid		Antifungal activity against *Colletotrichum gloeosporioides* with MIC 2.92 mol mL − 1	Elias et al. (2018)
		Cytochalasin D		Antifungal activity against *Colletotrichum gloeosporioides* with MIC 2.46 _mol mL − 1	
Phoma sp.	*Fucus serratus*	Phomalacton		Antibacterial, good antifungal and antialgal activities	Hussain et al. (2014)
		(3R)-5-hydroxymellein		Antifungal, antibacterial and algicidal properties	
		Emodin		Antibacterial, antifungal acivity and algicidal properties	

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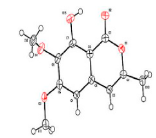
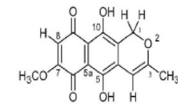
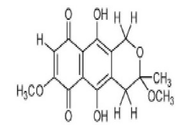
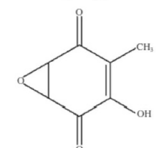
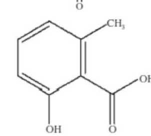
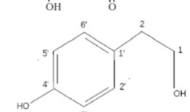
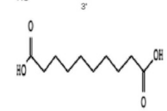
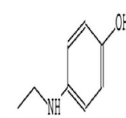
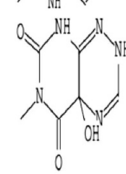
Table 2 (*continued*)

Fungal source	Host plant	Compound name	Structure	Activity against	References
Xylariaceae sp.	*Quercus gilva*	8-hydroxy-6,7-dimethoxy-3-methylisocoumarine		Alpha glucosidase inhibitors (Alpha glucosidase from *Saccharomyces cerevisiae) with* IC50 of 41.75 g/mL	Wheni and Tachibana (2017)
Cladosporium sp.	*Rauwolfia serpentina* (L.) Benth. ex Kurz.	Anhydrofusarubin		Cytotoxic effect	Huque et al. (2016)
		Methyl ether of fusarubin		Antibacterial activity against *Bacillus megaterium, Staphylococcus aureus, Pseudomonas aeruginosa* and *Escherichia coli* at the concentration of 40 g/disc	
Pseudocercospora sp.	*Elaeocarpus sylvestris*	Terreic acid		Antioxidant activity in DPPH radical scavenging with IC50 of (0.22 ± 0.02) mmol/L	Prihantini and Tachibana (2017)
		6-methylsalicylic acid		Antioxidant activity in DPPH radical scavenging with IC50 of (3.87 ± 0.27) mmol/L	
Diaporthe helianthi	*Luehea divaricata*	2 (−4 hydroxyphenyl)-ethanol (Tyrosol)		Antagonistic effects on *Staphylococcus aureus, Escherichia coli, Micrococcus luteus, Salmonella typhi, Enterococcus hirae* (human pathogenic bacteria) and *Phytopathogenic Xanthomonas asc. phaseoli*	Vânia Specian et al. (2012)
Trichoderma sp.	*Ocimum basilicum* L.	1,10 Decanedioic acid		Antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* with 20 mm and 32 mm zone of inhibition	Hateet (2017)
		Phenol, 4- (ethylamino)-4-Ethylaminophenol		Antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* with 24 mm and 19 mm zone of inhibition	
		Pyrimido [5,4-E]1,2,4-triazine-5,7 (4ah,6H)-dione,8,8a-dihydo4a-hydroxy-6-methyl-		The inhibition zone diameter of bacterial species *Staphylococcus aureus* and *Escherichia coli* respectively and 26 and 27 mm	

(*continued on next page*)

Table 2 (*continued*)

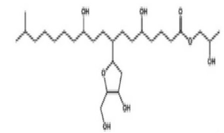
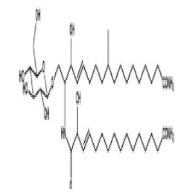
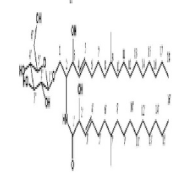
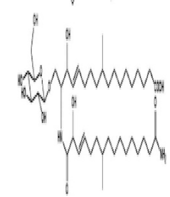
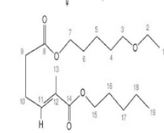
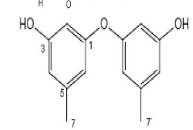
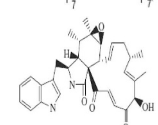
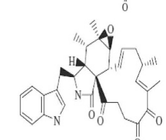
Fungal source	Host plant	Compound name	Structure	Activity against	References
Aspergillus niger sp.	*Calotropis procera*	3-hydroxypropyl 5, 11-dihydroxy-8- (4-hydroxy-5- (hydroxyl methyl) tetrahydrofuran-2-yl) 17-methyleoctadecanate		Antimicrobial activity	Verma et al. (2017)
		(E)-N1- ((E)-18-amino-3-hydroxy-9-methyl-18-oxo-1- (((2R, 3R, 4S, 5S, 6R)-3, 4, 5- trihydroxy-6- (hydroxymethyl) tetrahydro-2H-pyran-2-yl) oxy) octadec-4-en-2-yl)- 2- hydroxyhexadec-3-enediamide		Antimicrobial activity	
		(E)-N1- ((E)-18-amino-3-hydroxy-9-methyl-18-oxo-1- (((2R, 3R, 4S, 5S, 6R)-3, 4, 5- trihydroxy-6- (hydroxymethyl) tetrahydro-2H-pyran-2-yl) oxy) octadec-4-en-2-yl)-2- hydroxy-7-methylhexadec-3-enediamide		Antimicrobial activity	
		(E)-17- ((E)-16-amino-2-hydroxy-7-methyl-16-oxohexadec-3-enamido)-16-hydroxy-10- methyl-18- (2R, 3R, 4S, 5S, 6R)-3, 4, 5-trihydroxy-6- (hydroxymethyl) tetrahydro-2H-pyran- 2-yl) oxy) octadec-14- enoic acid		Antimicrobial activity	
Fusarium oxysporum	*Sclerocarya birrea*	6- (5-ethoxypentyl) 1-pentyl-2-methylhex-2-enedioate		Antimicrobial activity against *Staphylococcus aureus, Escherichia coli, Streptococcus pyogenes* and *Pseudomonas aeruginosa*	Garba et al. (2018)
Aspergillus flocculus	*Markhamia platycalyx*	Diorcinol		Diorcinol exhibited significant anti-trypanosomal activity with inhibition of 97%. towards *Trypanosoma brucei brucei* (the sleeping sickness causing parasite)	Tawfike et al. (2019)
Chaetomium globosum	Ginkgo biloba	Chaetoglobosins A		Both the compounds recorded with antibacterial activity against *Mucor miehei*	Yu et al. (2010)
		Chaetoglobosins C			

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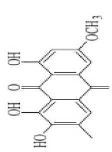
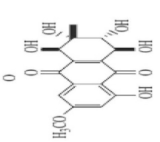
Table 2 (*continued*)

Fungal source	Host plant	Compound name	Structure	Activity against	References
Ampelomyces sp.	*Urospermumpicroides*	3-*O*-methylalaternin		Antimicrobial activity towards *Enterococcus faecalis*, *Staphylococcus epidermidis* and *Staphylococcus aureus* observed in both the compounds	Yu et al. (2010)
		Altersolanol A			

herbicides and insecticides are the pesticides used against pathogens, weeds and insects respectively (Silva et al., 2018). Rejection of non-target organisms, harming of farmers and food, soil, animals and water contamination are the environmental threats provoked due to the indiscriminate and intensive usage of pesticides in agriculture. The improper usage of pesticides makes the weeds, pest and phytopathogens insensitive to them (Stangarlin et al., 2011). Chemical fungicides have the fungicidal activity towards the pathogen and the host plant tissue and pathogen convert the fungicides to toxic by-products. Resistance to fungicide, the degradative effect on the ozone layer, high soil contamination and toxicity on microbial communities are the problems generated due to the extensive use of chemical fungicides. The use of the chemical in the controlling process is not efficient completely and the disease that remains to be persistent is rhizoctonia (Goudjal et al., 2014). The first and second generation fungicides consist of multisite inhibiting organic compounds with antifungal activity. Third generation fungicides consist of lower toxicity compounds that are site-specific used in fungal diseases control and are extremely active. As the phytopathogens develop the resistant, the site-specific becomes less effective (Silva et al., 2018).

Fungal diseases are controlled and managed by lots of different approaches, chemical usage is the favorite method for the farmers when compared to others. All over the world, plants diseases are the severe intimidation for the crops that are important economically and fungi, bacteria and viruses are the pathogens mainly responsible for causing diseases in plants. The excessive and continuous usage of chemicals leads to the development of newly resistant fungal pathogens which is the major problem (Adnan et al., 2019). The complex pathogenic agents in root-rot diseases make the disease uncontrollable by few biocontrol methods and various chemical pesticides. The ecological functions of fungal endophyte are complex that needs to be exploited more and these group of microorganisms are poorly inspected one (Zheng et al., 2017). The development of fungicides resistant fungal strains leads to the failure of controlling disease and due to strict EU regulations, the number of fungicides being used in agriculture are withdrawn. For effective and sustainable control, there is a need for an alternative controlling approach. The individual and integrative use of the physical, chemical, biological, cultural method and host plant with resistant varieties are the control strategies available for managing diseases (Malandrakis et al., 2018).

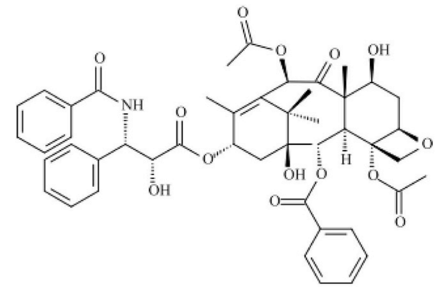
The efficient nutrient utility, strong reproductivity, the capacity for rhizosphere alteration and plant growth promoting activities makes the Trichoderma as the promising antagonist against plant pathogenic fungi and their also capable to survive in the various adverse environmental conditions (Adnan et al., 2019). By the exclusion, eradication, protection of crop and sanitation, the bacterial pathogens that affect the plant can be controlled. The occurrence of the disease can be lowered by the reliable method of prohibiting the spreading of pathogens while treating the plant's disease is challenging. The pollution in the environment and the loss of yield can be minimized by using numerous compatible methods as integrated and it also retains stable crop production. From primary research to the molecular mechanism of biological control and pathogens leads to the discovery of chemical compounds and natural products that further progress to "biorational" pesticides (Arwiyanto, 2019). *Fusarium oxysporum* (nonpathogenic), *Agrobacterium tumefaciens, Pythium oligandrum, Beauvaria bassiana, Metarrhizium anisopliae, Chaetomium globosum, Verticillium chlamydosporium* are the few agents registered in Central Insecticide Board (CIB) to be used for biocontrol of phytopathogens (SINGH, 2014). Lots of fungicides have deregistered due to their impact on the environment and their residues in food. In recent decades, the practice of Biological agent became the alternative controlling method in plant diseases (O'Brien, 2017). About 100% of disease was suppressed by utilization of fungicide on the apple affected with *Phytophthora cactorum*, at the same time the suppression of disease level ranges between 79% to 98% based on the application of diverse BCA (O'Brien, 2017). Trichoderma spp. is reported to act as biological control agents in lowering the occurrence of root diseases which was induced by soil borne pathogenic fungi (Cao et al., 2009).

8. Bioactive natural compounds production by endophytes

Endophytic fungi have symbiotic relationships with the host plants and may have the capability to produce bioactive metabolites with significant pharmacological activities. Many commercially available human medicines are developed from the secondary metabolites of microbial sources. Nowadays, discovering novel biochemical compounds with antibacterial activity plays an important role in developing new drugs (Wu et al., 2018). Environmental factors can extremely influence the biosynthesis of microbial secondary metabolites. The secondary metabolisms are controlled by the regulatory events, that are generated by the additions of inducer or reduced growth rate or by nutrient deficiency. The production of metabolite and microorganisms growth can be influenced by altering chemical and physical factors, that is a useful screening process and this may also lead to the better utilization of microbes with commercial importance (Astuti et al., 2017). Plant endophytic fungi play a vital role in producing secondary metabolites with anti-tumor, antiviral, insecticidal, antioxidant and antimicrobial activity. They live within plant tissues asymptomatically without causing any serious infections and also they have the capability to synthesize bioactive compounds as the same or similar to their host (Lou et al., 2016). The bioactive compounds from the medicinal plants are efficient in preventing or treating the diseases and the plant furnishes a unique environment for their endophytes (Elgorban et al., 2018).

An alkaloid compound asperfumoid was isolated from *Aspergillus fumigatus* CY018, An endophytic fungi of *Cynodon dactylon* (Zhang et al., 2012). Sterigmatocystin, averantin, methylaverantin and nidurufin are the cytotoxic compound extracted from *Aspergillus Versicolor* fungus harbored in Petrosia sp. and the other fungus Penicillium sp. of *Limonium tubiflorum* produced 11a-methoxycurvularin 4, 11b-methoxycurvularin, 1-chloro-2,4-dihydroxy-5-methoxy-7-methylanthraquinone, dehydrocurvularin 6 with cytotoxicity (Uzma et al., 2018). (−)-6-deoxyoxysporidinone, joxysporidinone and (−)-4,6′-anhydrooxysporidinone are the pyridines compound isolated from *Cladosporium herbarum,* the endophytes of *Ephedra fasciculate* (Zhang et al., 2012). *Trichoderma brevicompactum,* an endophytic fungus strain isolated from garlic and trichodermin (4β-acetoxy-12,13-epoxy-Δ^9-trichothecene) is the antifungal compound from the fungus showed antifungal activity against *Rhizoctonia solani* and *Botrytis cinerea* with EC50 of 0.25 μgmL^{-1}and 2.02 μgmL$^{-1.}$ (Shentu et al., 2014). Phomoenamide, a new alkaloid compound from *Phomopis* sp. PUS-D15 of *Garcinia dulcis* Kuiz. and alantryleunone, alantrypinene, alantryleunone are the quinazolines from *Eupenicillium* sp. of *Murraya paniculata* leaves are few novel alkaloids reported as the secondary metabolites produced from fungal endophytes (Zhang et al., 2012).

Taxus brevifolia commonly known as pacific yew tree produces paclitaxel, a highly functionalized diterpene that is used as an anticancer drug and their endophytes of different species from Pestalotiopsis genus also capable to produce the same compound in low yields. Endophytic fungi produce numerous metabolites with commercial potentials and biological activity towards different cancer cell lines (Astuti et al., 2017). Some of the compounds isolated from endophytes are reported to be identical as their host compounds (Song et al., 2017). L-arginine deiminase, gliotoxin, 2,14-dihydrox-7-drimen-12,11-olide, TMC 256 A1, monomeric naphtho-g-pyrones, brefeldin and nigerasterols A and B are the bioactive compounds with anticancer activity produced by Aspergillus, a filamentous fungus which is the second highest compounds producing fungal endophyte (Astuti et al., 2017). As suggested from the early studies, bioactive compounds of endophytes could be the alternative source for discovering the novel drugs in cancer treatment. Taxol, which belongs to the class of taxanes is a highly functionalized polycyclic diterpenoid used in the treatment of various human cancer and it is first anticancer drug in the world. In the clinical practice, a few anticancer drugs from a plant source such as vinblastine, topotecan, etoposide, irinotecan, taxol and vincristine are used for treating different types of human cancers. As predicted in the year of 2000, 57% of natural products and their by-product based compounds are analyzed in the clinical trials of cancer therapy (Uzma et al., 2018).



Taxol (paclitaxel) (Zhao et al., 2010)

Cercosporenes, aspterpenacids and phomopchalasins are the new bioactive compounds isolated from fungal endophytes in recent times. Natural sources provide more diverse structures when compared to the libraries of synthetic and combinatorial compounds (Song et al., 2017). In the future, for the development of drugs ergosterol derivatives can be a good feasible lead. Fusarium sp. were reported to produce diverse classes of metabolites and ergosterol derivatives (Khayat et al., 2019). The secondary metabolites from the endophytic community of the plant can provide beneficial characteristics for their host and the traditionally used medicine plants are the great source for endophytic fungal strains with novel bioactive metabolites (Venkateswarulu et al., 2018). According to the latest reports, the chemical constituents in the host plant can be metabolized by their fungal endophytes. New chemicals discovered from the endophytic fungi are the origin of many new bioactive natural product and the chemicals have the ability to be straightly used as drugs (Zhang et al., 2016). Patulin, isopestacin, pestacin and sordarcin derivative are few antimicrobial compounds derived from plant-associated fungal endophytes (Jalgaonwala et al., 2011). Ergosterol, terminatone, 4hydroxy benzaldehyde and 4-hydroxy-octadec-6-enoic acid ethyl ester are extracted from the crude ethyl acetate extract of *Penicillium thiomii*, an endophyte of *Terminalia chebula* Retz (Shoeb et al., 2014). Pestalachloride A and pestalachloride B are the novel antibiotics isolated from *Pestalotiopsis adusta* of *Saurauia scaberrinae* showed antifungal activity towards plant pathogens such as *Verticillium aiboatrum, Gibberella zeae* and *Fusarium culmorum* (Yu et al., 2010).

Human cytomegalovirus (hCMV) protease are inhibited by the compounds cytonic acid A and cytonic acid B which is isolated from the endophytic fungi of Cytonaema sp. Several endophytic fungi are recorded to produce several antiviral agents (Jalgaonwala et al., 2011). 5-hydroxy-4-hydroxymethyl-2H-pyran-2-one and (5-hydroxy-2-oxo-2H pyran-4-yl) methyl acetate are the two novel lactone derivatives isolated from the endophyte Trichoderma sp. of *Tinaspora crispa* (Elfita et al., 2014). An endophytic fungal strain pezicula produces (+)-cryptosporiopsin and (−) mycorrhizin A that are chlorinated metabolites has the ability to be used as antibacterial, algicidal, herbicidal and fungicidal agent. Syringin and coniferin are the two monolignol glucosides produced by both the endophyte Xylariaceae species and the host plant (Joseph and Priya, 2011). Tenllone I, lithocarins B, lithocarins C, lithocarin D, tenellone H and phomopene are the compounds isolated from *Diaporthe lithocarpus*, an endophytic fungus of a medicinal plant *Morinda Officinalis*. Among them lithocarins B, lithocarins C and tenellone H showed cytotoxic activity towards A549,SF-268, HepG-2, and MCF-7 tumor cell lines (Liu et al., 2019).

9. Conclusion

Fungal endophytes are a rich source of novel compounds with potent biological activities in agriculture and medical sector. The discovery of novel secondary metabolites with pharmacological activities from the fungal endophytes might be useful in the development of a new drug. The production of bioactive secondary metabolites by plant-associated fungal endophytes and their capability to act as biocontrol agents are highlighted in this review.

For sustainable agriculture, the management and control of plant disease are very crucial and the use of endophytes are the alternative approach for using chemical pesticides. The soilborne fungi remain alive in the soil as saprophytes for a long time and have a wide range of host plants. The control of plant disease is very difficult, in case of soilborne fungi pathogens. The main limitation for using resistant cultivars is that they are available for some particular combination of host and pathogen. As chemical pesticides are harmful to both human and environment, the endophytes based biocontrol agents could be a very promising approach in plant disease control. Trichoderma species, an endophyte species is well known for its biocontrol activity towards plant diseases. Chaetomium sp. and Trichoderma sp. are the fungal endophyte has the ability to reduce the rice brown spot disease and enhance the plant growth. The molecular identification and biological characterization of potent microbes help us to understand their antagonistic mechanism and they use of endophytic microbes as a biocontrol agent and bioactive compounds producer has a great impact on eco-compatible and modern agriculture.

Future work is needed to be conducted on the antagonistic activity of endophytic fungi and to produce commercial biocontrol agent for controlling phytopathogens. The researcher's attention towards the bioactive secondary metabolites producing and plant growth-promoting endophytes has increased a lot, as they are the abundant source for discovering new medicines and as the ecofriendly plant protector.

Acknowledgement

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