Review Article

Fungal Endophytes: A Blooming Reservoir for Future Products

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ABSTRACT

Endophytic fungi isolated from plants serve as a significant and novel source of biotherapeutic compounds with their potential application in several fields. As plant sources are widely investigated as new chemical existence in therapeutic purposes, so endophytes residing inside it also contribute to being a significant source for drug discovery. Currently, human faces a lot of challenges for surviving due to the emergence of unknown diseases, infections and also resistance to drugs in the ecosystem. So, demand has been increased in the medicinal field for the requirement of bioactive compounds productions. To overcome these, endophytes can be considered as an alternative potential source. Different types of endophytes exist, in which fungi are considered to be a rarely unexplored microorganism as it is a reservoir of largely unexploited bioactive metabolites. This review mainly focused on the ecofriendly relationship with their host and also its biotherapeutic potential in treating several diseases.

Keywords: Novel compounds, biological activities, medicinal plants, applications, host-endophytes interaction.

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INTRODUCTION

Fungi are considered to be the second largest group of organism after insects with great biodiversity and key component of tropical ecosystems throughout the world.[1] Endophytic fungi are the most frequently studied group compare to other microbial study, as it is considered to be outstanding source for producing biotherapeutic natural products and also it act as the biocontrol agent to the host.[3] Microbes can serve as reliable, reproducible, and inexhaustible origin of novel metabolites with pharmaceutical potential.[5] In spite of the fact that the technologies have been improved, approximately 80% of the world population residing in developing countries rely on herbal medicines for their primary healthcare system.[7] Recent studies found that bacterial infection seems to play important role in chronic disease and eventually leads to fatality. Increases of drug resistance towards microbes create a larger threat to the health of the growing world population, so it is necessary to search for new antibiotics from natural sources.[8,9]This review highlights that the unknown and/or underexplored sources of biological diversity are often interrelated with novel chemical diversity. So, the researcher should take into account that endophytes are considered to be unexploited sources of natural products and also it is rich in novel bioactive compounds productions.[11]

Bioactive compounds can be obtained from different ways like extraction from natural, microbial via fermentation and also via a microbial transformation. Some disadvantages exist while extracting metabolites from natural sources such as climatic variation and ecological problems, thus there is a requirement of innovative approaches for obtaining such compounds.[12] Despite that, increasing rate of environmental degradation and deterioration of land and water resources by climate change, usage of toxic insecticides and discharge of industrial effluents have directed to the loss of biodiversity, mainly of plant species.[13] Therefore, biotechnological techniques could be a promising alternative method for establishing an inexhaustible, economical and renewable resource of metbolites.[12]Different metabolites are isolating from endophytic fungi which acts as the potential therapeutic agents for treating several disease and also it is useful in agriculture and food industries.[14,16] Several scientists have started to research on fungal endophytes as it considered to be the potential producers of novel biotherapeutic compounds, and also it is the first microorganism for the discovery of "gold" bioactive compound (taxol) from *Taxomyces andreanae* in 1993.[17]The research study says that naturally derived products has the capacity to fight against microbial pathogens, thus this makes the research communities to search for natural antimycobacterials for treating patients with tuberculosis which is considered to be deadly infectious diseases in human population.[7]Extinction of natural diversity especially plant species would be reduced by investigation of medicinal plants as a source for bioactive compounds. Biodiversity and sustainable ecosystem can be maintained by increasing biotechnological application in extracting bioactive compounds from endophytic fungi. Production

of metabolites through fermentation has several advantages as it considered to be fast, reproducible and seasoning independent.[18]

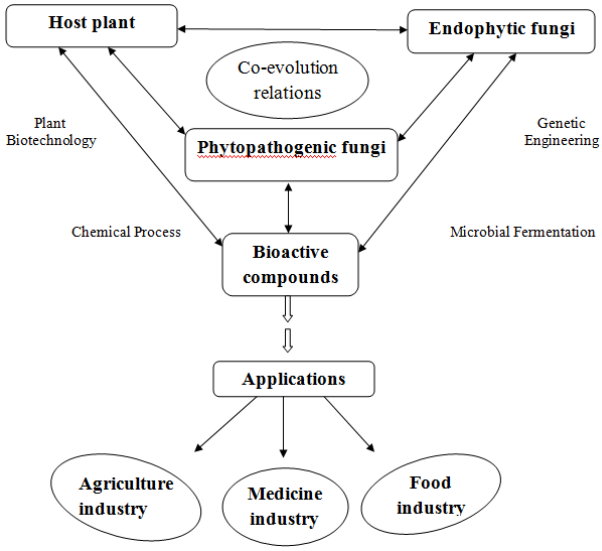


Figure 1: Symbiotic relationship that exist between plant-endophytic fungi in bioactive compound production and its industrial application [2]

The previous study reported that some of the natural products like antibiotics, anticancer and also other compounds with different functional roles are obtained from endophytes. So endophytic fungi have increased attention in the production of novel compounds and also several research studies have proven that novel natural products discovered from it are utilizing in medicinal, industry and agriculture purpose.[19-21]

Host - endophytes relationship

The symbiotic relationship that exists between the host plants and endophytes makes this organism to have special biochemical metabolic pathways in comparison to other metabolic pathways as shown in Figure 1.[6] The research study reported that endophytic fungi infected plants are habitually healthier than endophyte free ones.[4]The relationship that exists between host to host and endophytic fungi may vary. The research study presented that the relationship that exciting between host plant and endophytic fungi has the ability to balance infectious agent host antagonism not actually symbiotic one. [64]

Role of endophytic fungi as a biocontrol agent

Endophytes are the microorganisms that resists in the internal plant tissues within the few weeks of leaf emergence underneath the epidermal cell layers has a biocontrol agent.[22,1]By residing inside the plant tissue, endophytes generally get nutritions as well as protection and in return, endophytes produces functional metabolites as a protection to the host plants.[3] The relationship that exist between plant and endophytes is identified to be mutualistic, in which the former acts as the defender and feeder for the latter.[5]Secondary metabolites produce by endophytes protects plant against pests, pathogenic organisms, insects and herbivores[25](Figure 2). There may be a chance of causing toxic effects in human by the synthetic drugs produced by pharmaceutical industry but the secondary metabolites extracted from endophytic fungi exhibits less toxicity towards higher organisms.[20]

Production of natural products by endophytic fungi

Pharmaceutical biology said that plants are considered to be 'bio-factories' of valuable therapeutic compounds, but due to the slow growing rate and collecting of rare endangered species create threats and imbalance in the plant diversity.[26]This can be overcome from the unexplored group of microorganisms, endophytic fungi.[1]Molecules obtained from the natural products of medicinal plants and microorganisms have found to be an excellent source for providing novel compounds in pharmaceutical products development. The higher chance of gaining novel compounds is higher from a novel source, endophytic microbes.[28]Bioactive substance produce by the endophytes has been directly related to the host microorganisms evolution; by this, it incorporate genetic information's from higher plants, permitting them to better adapt to the host plant and execute various functions like protection against pathogens, insects and grazing animals.[29]There is an ever-growing need for new and useful bioactive compounds to afford support and relief in all aspects of human conditions such as the emergence of life threading viruses, drug resistance in bacteria and incredible increase in the occurrence of fungal infections around the world population.[30]Almost every plant species are the host to diverse fungi with varying in their content in their plant tissues known as endophytes. In fact, a current study says that 51% of the bioactive substances extracted from endophytic fungi were previously unidentified.[31]The structure of newly isolated metabolites is tabulated in Table 1

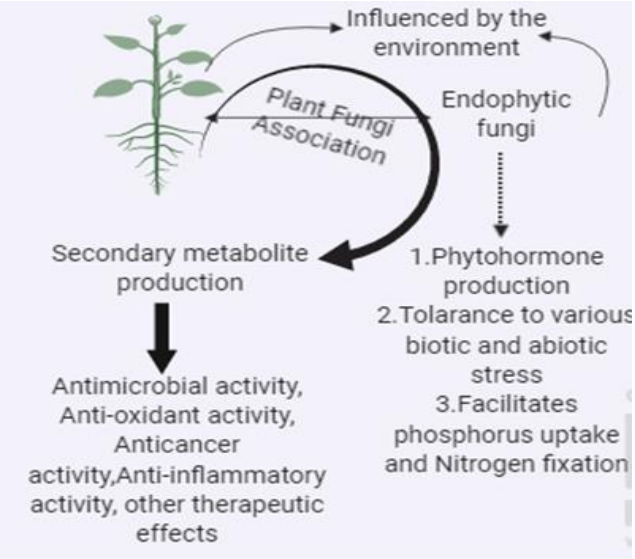


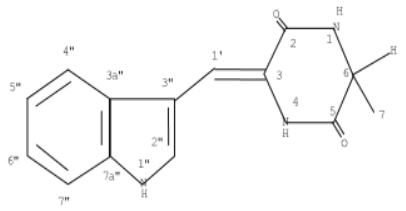
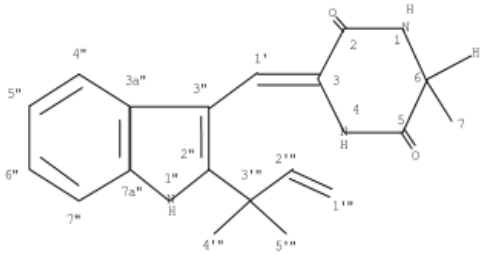
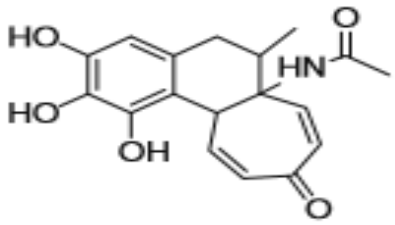
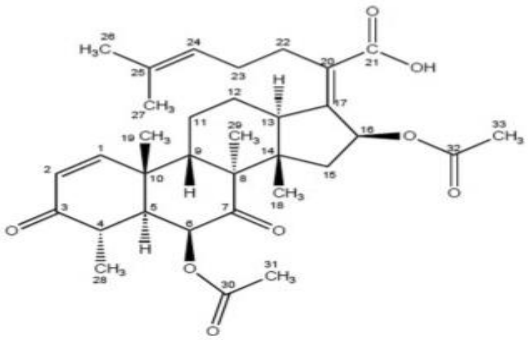
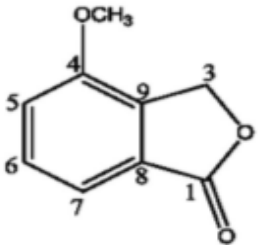
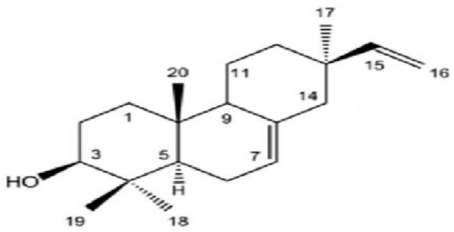
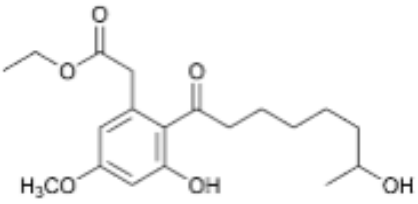
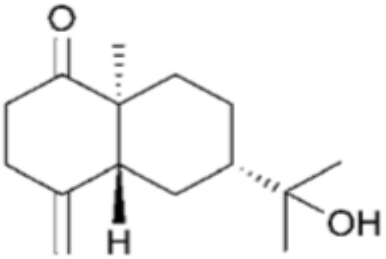
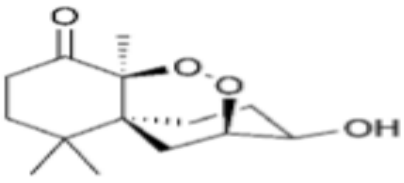
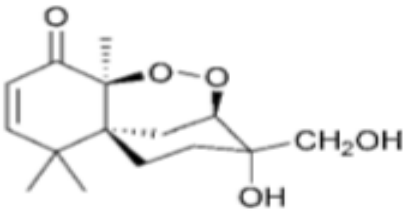
Figure 2: Mechanism of plant growth promotion and bioactive compounds production from endophytic fungi

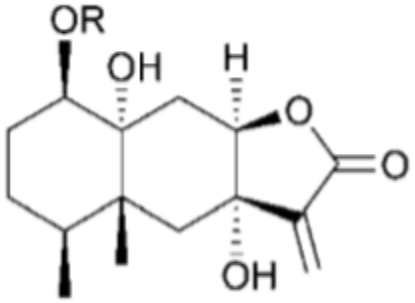
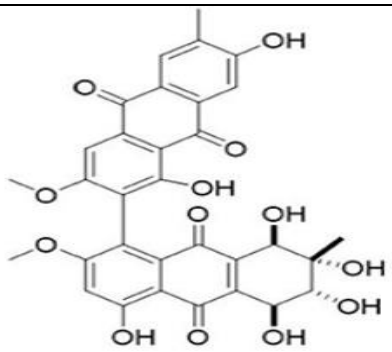
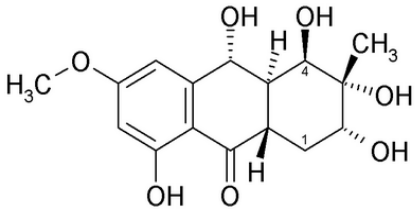
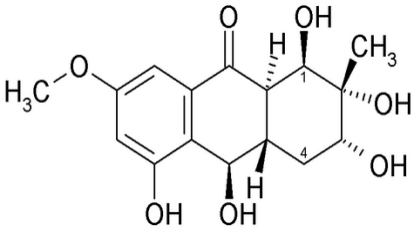
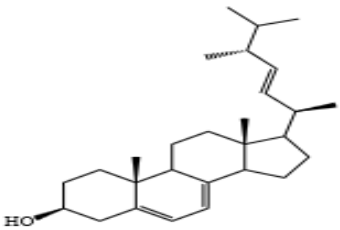
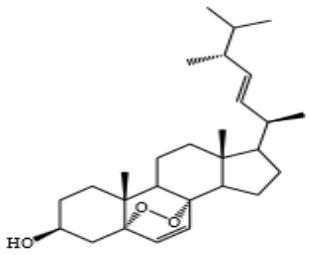
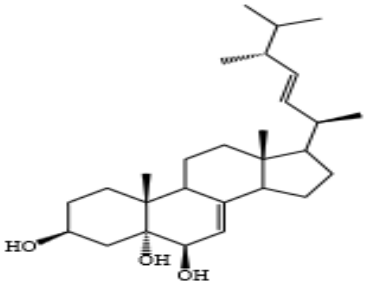
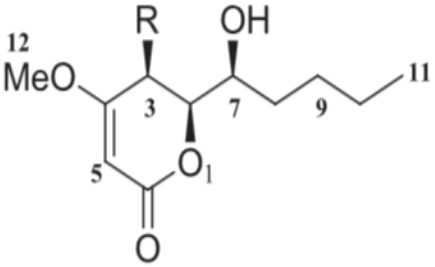
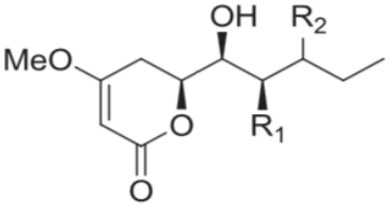
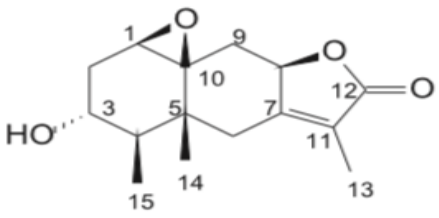
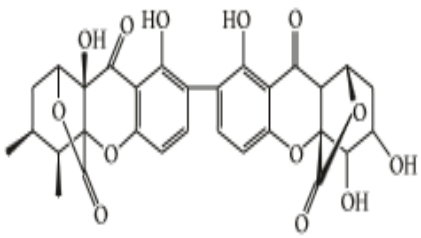
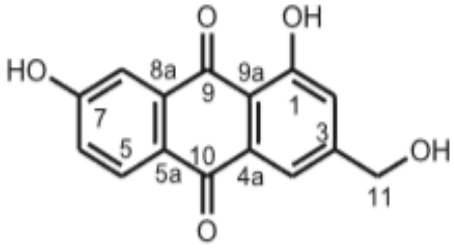
Therapeutic drugs can be developed by identifying bioactive compounds from endophytic fungi which are

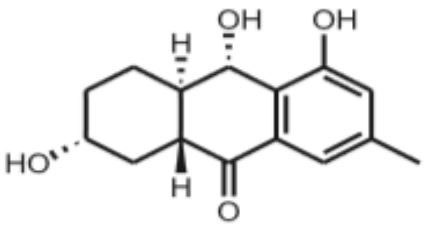
considered to be highly effective, less toxic and having insignificant environmental impact.[32–34]There is an increasing realization of the enormous range of biomolecules produced by different group of endophytic fungi, which can either be assigned as bioactive and/or chemically novel molecules or it can be generally classified as alkaloids, tetralones, xanthones, quinines, benzopyranones, phenols, isocoumarins etc,.[21,35] (Table 2)

As a result endophytes provide several advantageous and novel prospective of biotherapeutic compounds over chemically synthesized compounds, this made the researcher towards the discovery of microbial metabolites. Therefore, identifying and characterizing of natural products from endophytic fungi will always be a novel and potential requirement in various fields.[9]

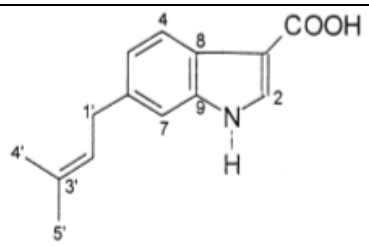
Table 1: Some of the newly isolated biotherapeutic compounds from fungal endophytes

 Dipodazine[10]	 (3,1'-didehydro-3[2''(3''',3'''-dimethyl-prop-2- enyl)-3''-indolylmethylene]-6-methyl pipera-zine-2,5-dione)[10]
 6-Methyl-1,2,3-trihydroxy-7,8-cyclohepta-9,12-diene- 11-one-5,6,7,8-tetralene-7-acetamide[5]	 Helvolic acid[58]
 4-methoxy-1(3H)-isobenzofuranone[43]	 Pimara-7,15-dien-3β-ol diterpene[44]
 2-(70-hydroxyoxooctyl)-3-hydroxy-5-methoxy-benzene acetic acid ethyl ester[59]	 Ent- 4(15)-eudesmen-11-ol-1-one[59]
 Merulin A[59]	 Merulin C[59]

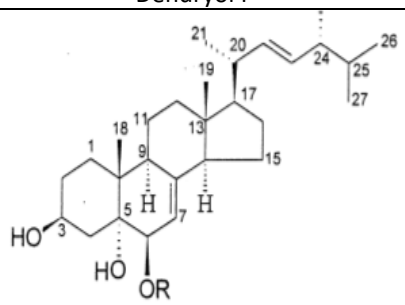
 Eremophilane[59]	 Alterporriol G[47]
 Altersolanol K[47]	 Altersolanol L[47]
 Ergosta-5,7,22-trienol[50]	 5α,8α-epidi- oxyergosta-6,22-dien-3β-ol[50]
 Ergosta-7,22-dien-3β,5α,6β-triol[50]	 Photipyrones A[51]
 Photipyrones B[51]	 Cupressolide A[60]
 Ergoflavin[12]	 1,7-dihydroxy-3-hydroxymethyl-9,10-anthraquinone[61]



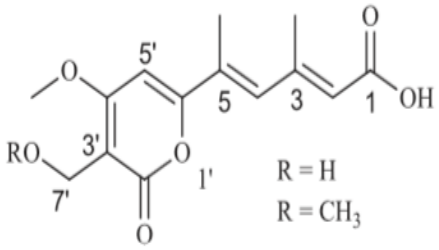
Dendryol F[61]



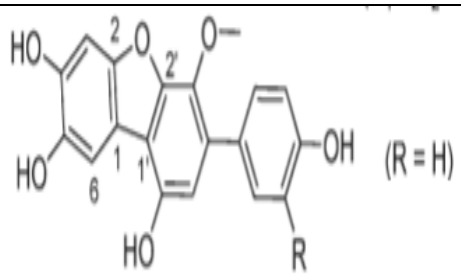
Isoprenylindole- 3 -carboxylic acid[57]



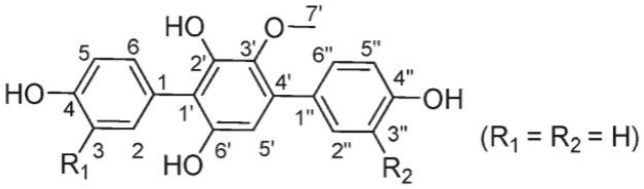
3 β, 5 α-Dihydroxy- 6 β-acetoxy-ergosta- 7 , 22 –diene[57]



Infectopyrones A and B[62]



3''-deoxy-6'-O desmethylcandidusin B[63]



6'-O-desmethylterphenyllin[63]

Table 2: List of bioactive compounds produced by endophytic fungi and their applications

Host plant	Endophytic fungi	Chemical compound	Application	Reference
Podophyllum peltatum	*Phialocephala fortinii*	Podophyllotoxin	Anticancer activity	16
Luehea divaricata	*Diaporthe helianthi*	2(-4 hydroxyphenyl)-ethanol	Antibacterial activity	36
Sclerocarya birrea	SB7-FO-F10	6-(5-ethoxypentyl) 1-pentyl-2-methylhex-2-enedioate.	Antibacterial activity	25
Apodytes dimidiata	*Fusarium solani*	Camptothecin	Antitumor activity	16
Nothapodytes foetida.	*Neurospora sp.*	Camptothecin	Antitumor activity	16
Melia azedaracha	*Penicillium janthinellum*	Polyketide citrinin	Antibacterial activity	14
Garcinia sp.	*Phomopsis sp*	Phomoxanthone A and B	Antitubercular activity	14
Taxus brevifolia	*Taxomyces andreanae*	Paclitaxel	Anticancer activity	17
Sinopodophyllum hexandrum	*Trametes hirsuta*	Podophyllotoxin	Anticancer, antiviral, and anti-rheumatic properties	17
Torreya taxifoli	*P. microspora*	Pestaloside, β- glucoside, pestalopyrone and hydroxyp- estalopyrone	Antifungal activity	30
Bontia daphnoides	*Nodulisporium sp*	Nodulisporicacids	Insecticidal Activities	25
Artemisia mongolica	*Colletotrichum gloeosporioides*	Colletotric acid	Antimicrobial activity	37
Erythrina cristagalli	*Phomopsis sp*	Phomol	Antifungal and antibacterial activity	37
Justicia gendarussa	*Colletotrichum gloeosporioides*	Taxol	Anticancer activity	38

Moringa oleifera	*Nigrospora sp*	Griseofulvin, dechlorogriseofulvin and mellein	Antifungal activity	39
Porteresia coarctata	*Penicillium chrysogenum*	Diketopiperazine	Antibacterial activity	10
Cinnamomum mollissimum	unknown	5-hydroxyramulosin	Antifungal and anticancer activity	40
Gloriosa superba	*Aspergillus species*	5-(hydroxymethyl) furan-2-carbaldehyde, 4-hydroxy-phthalic acid-dimethyl ester	Antimicrobial and cytotoxic activity	5
Annona squamosa	*Penicillium sp.*	Meleargrine and Chrysogine	Antibacterial and anticancer activity	2
Paris polyphylla var. yunnanensis	*Pichia guilliermondii*	Ergosta-5,7, 22-trienol, 5α,8α-epidioxyergosta-6, 22- dien-3β-ol, ergosta-7, 22-dien-3β,5α,6β-triol	Antibacterial activity	2
Aegiceras corniculatum	*Emericella sp.*	Aegiceras corniculatum	Anti-viral activity	2
Eucommia ulmoides	*Sordariomycetes sp*	Chlorogenic acid	Antimicrobial, antitumor and anti-oxidant activity	41
Aegiceras corniculatum	*Penicillium sp*	Polketides, leptusphaerone Penicillenone, 9-demethyl FR-901235 and leptosphaerone C	Cytotoxicity activity	42
Forsythia viridissima	*Pezicula sp.*	Mellein	Antifungal activity	43
Smallanthus sonchifolius	*Nigrospora sphaerica*	Pimara-7,15-dien-3β-ol and ergosterol per- oxide	Cytotoxicity activity	44
Smallanthus sonchifolius	*Pemphigus betae*	(22E,24R)-ergosta-4,6,8(14),22-tetraen-3-one and 8-hydroxy-6-methoxy-3-methyl-isocoumarin	Anticancer activity	44
Platycladus orientalis	*Phyllosticta spinarum*	Tauranin	Anticancer activity	45
Juniperus communis	*Aspergillus fumigatus*	Deoxypodophyllotoxin	Anticancer agent	45
Cistus monspeliensis	*Phomopsis sp.*	Chromones, phomotenone and phomochromones A and B	Antibacterial activity	46
Mentha pulegium	*Stemphylium globuliferum*	6-O-methylalaternin,macrosporin, altersolanol A, altersolanol J, altersolanol K and altersolanol L	Cytotoxicity activity	47
Opuntia dillenii	*Fusarium sp.*	Equisetin	Antibacterial activity	48
Piper longum	*Periconia sp.*	5-(3, 4-methylenedioxyphenyl)-1-piperidinopent-2, 4-dien-1-one)	Antibacterial activity	49
Paris polyphylla	*Pichia guilliermondii*	Helvolic acid	Antibacterial and anticancer activity	50
Paris polyphylla	*Pichia guilliermondii*	5α,8α-epidioxyergosta-6,22- dien-3β-ol	Antibacterial activity	50
Plumeria acutifolia	*Phomopsis sp*	Terpenoid	Antibacterial activity	15
Melia azedarach	*Penicillium brasilianum*	Phenylpropanoids	Anticancer, antioxidant, antimicrobial, anti-inflammatory and immunosuppressive properties	19

Bontia daphnoides	*Nodulisporium sp.*	Nodulisporic	Insecticidal effect	19
Roystonea regia	*Pestalotiopsis photiniae*	Photipyrones A and B	Cytotoxicity activity	51
Platycladus orientalis	*Phyllosticta spinarum*	Tauranin	Anticancer activity	52
Trachelospermum jasminoides	*Myrothecium roridum*	10,13-cyclotrichothecane-derived macrolide myrothecine C	Anticancer activity	52
Artemisia annua	*Myrothecium roridum*	Myrothecines, A and B	Anticancer activity	52
Torreya taxifolia	*Pestalotiopsis microspora*	Ambuic acid	Antibacterial activity	26
Cyndon dactylon	*Aspergillus niger*	Rubrofusarin B	Antitumor activity	26
Roystonea regia	*Pestalotiopsis photiniae*	Photinides A -F	Antitumor activity	26
Solanum xanthocarpum	*Phomopsis vexans*	Lovastatin	Hyper-cholesterolemic and hypolipaemic properties	53
Dicerandra frutescens	*Phomopsis longicolla*	Dicerandrols A–C	Antibacterial activity	11
Catharanthus roseus	*Mycelia sterilia*	Vincristine	Anticancer activity	11
Melia azedarach	*Penicillium brasilianum*	Phenylpropanoids	Anticancer, antioxidant, antimicrobial, anti-inflammatory, and immuno-suppressive properties	12
Curcuma amada	*Fusarium oxysporum*	2,3-pentanediol	Antiaging effects	21
Aegle marmelos	*Bartalinia robillardoides*	Taxol	Anticancer activity	54
Pteris pellucida	*Emericiella quadrilineata*	Benzyl benzoate	Antibacterial activity	9
Gastrodia elata	*Mycena dendrobii*	Indoleacetic acid	Pant growth promotion	55
Salvia miltiorrhiza	*Trichoderma atroviride*	Tanshinone IIA and tanshinone I	Antibacterial and anti-inflammatory activity	55
Ginkgo biloba	*Fusarium oxysporum*	Ginkgolide B	Antishock, antiallergic, and anti-inflammatory activity	55
Arbutus unedo	*Talaromyces pinophilus*	Herquline B	Anti-aggregation factor	56
Artemisia annua	*Colletotrichum sp.*	6-isoprenylindole-3-carboxylic acid	Antibacterial activity	57
Artemisia annua	*Colletotrichum sp.*	3b,5a-dihydroxy-6b-acetoxy-ergosta-7,22-diene	Antifungal activity	57
Artemisia annua	*Colletotrichum sp.*	3b-hydroxy-ergosta-5-ene	Plant growth promotor	57

CONCLUSION AND PERSPECTIVES

As huge interest was shown in plants, scientists have started identifying biotherapeutic compounds from endophytic fungi which satisfies the demand of pharmaceutical industries. Endophytes provide several advantages to their host plants by increasing drug resistance; enhance the ability of plants to withstand environmental stresses, plant growth stimulation and nutrition recycles. It is essential to review and highlight the previous report, current research and up to date developments in research linked with endophytes to make the attention of the researcher toward this developing field and bringing out their hidden world for therapeutic uses in different fields such as medical, food and cosmetics. The study concludes that a rich source of novel compounds can be obtained from endophytes with a broad spectrum of bioactivities and diverse structural diversity. The bioactive compounds isolated from endophytic fungi showed the potential application in medicine, agriculture and food industry.

In summary, endophytic fungi isolated from plants are considered to be a novel and significant microbial source for discovering biologically active compounds primarily from their hosts; this makes several researchers to work on endophytic fungi. Biodiversity and drug resistance can be conserved by considering endophytes as an alternative drug source. As a result, traditional ways of drug discovery can be enhanced by utilizing endophytic fungi. Thereby, in future, by applying more innovative biotechnological tools for understanding the plant-endophyte interaction will result in the production of more novel bioactive compounds and also the detailed mechanism can be studied. In conclusion, this review provides recent understandings in improvement of novel secondary metabolites isolation with clinical benefits which can be additionally enhanced by researching endophytes further as these play a significant key front line role in the treatment of several diseases.

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