Shades of endophytic fungi: Exceptional plant inhabitants with *de facto* therapeutic promises

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Received 14th January 2021 / Accepted 25th August 2021

Abstract. From the tropics to the arctic, almost all living plants on the earth are resided by endophytic fungi. The microorganism can be found near intercellular or intracellular tissues and cause void adverse symptoms of infection. Endophytes and host plants are synergistically protecting each other. As the host provides nutrients, the endophytes serve the host by activating their defense mode against parasites and pests. A search for alternative drugs, mostly from natural sources, is in ascending trends due to the increase of lethal diseases. This review emphasizes the significance of several endophytic fungi as a foundation for novel bioactive sources which might be advantageous for human health. The communication between the endophytic fungi and their host has generated numerous unique bioactive metabolites from different biosynthetic pathways. These include ketones, polyketides, alkaloids, non-alkaloids, acids, coumarins, etc., which comprise numerous potent biological activities including antimicrobial, anticancer, antioxidant, insecticidal, antidiabetic, immunosuppressive, anti-arthritis, anti-inflammatory, and anti hypercholesterolemic. Around 1.5 million endophytic fungal species have been estimated. However, to date, only 100,000 species are reported. Thus, a few isolated compounds and their biological activities have been opted in this current review. All compounds were discovered from endophytic fungi, which resided on various host plants, particularly from algae to a higher family plant such as mangroves.

Keywords: endophytic fungi, medicinal plants, secondary metabolite, biological activity

INTRODUCTION

Up to 80% of the people in Asia, Latin America, and Africa use their local plants to treat numerous diseases (Maghrani *et al.*, 2005). In general, the survival of the plants relates to their physical and chemical defense system. During the unfavorable changes, the plants are forced to synthesize unique substances, which researchers enunciated as secondary metabolites, bioactive compounds, or natural products. The production of these compounds can be mimicked by the microbial inhabitant of the host plant, which is known as endophytes. They are a valuable source of new chemicals with possible usages in the medicinal,

agricultural, and industrial sectors (Hyde & Soyong, 2008). It has been reported by Sharma *et al.* (2020) that 46% of pharmacological activity from endophytes is the antimicrobial agent. It is followed by anticancer (40%), antioxidant (16%), anti-inflammatory (12%) and toxicity against brine shrimp (8%). The research on novel therapeutic compounds using endophytes was triggered by Martinus Willem Beijerinck during his important finding on root nodule bacteria, which can fix atmospheric nitrogen (Hardoim *et al.*, 2008). Since then, a number of reports on biological activities of secondary metabolites

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originated from endophytes were vastly recognized.

Endophytic fungal research has received much attention recently. Endophytic fungi are capable to colonize the terrestrial plants worldwide. They are discovered in plants growing in the humid and seasonal wet tropics, temperate environments, and boreal forests, ranging from extreme arctic to tropical forests. The fungi have been isolated from several angiosperms, gymnosperms, bryophytes and tracheophytes (Rodriguez *et al.*, 2009). Hawksworth (1991) estimated that about 100,000 species out of 1.5 million endophytic fungi had been reported. Endophyte-free plants are very rarely reported. The discovery of endophytes was relatively early, but little recognition has been done. Most of the reports put a special highlight on plant-endophytes interaction. In many cases, antimicrobial actives produced by endophytic fungi have been related to dominate a broad spectrum of chemical classes, such as ketones, polyketides, alkaloids, non-alkaloids, acids, coumarins, and etc. In general, these actives have been related to several mechanisms of action in order to perform their antimicrobial activity against pathogens. For instance, the actives own the ability to affect cell division, inhibit the enzyme production by microbes, disrupt the microbial membrane and alter virulence genes (Khameneh *et al.*, 2019; Othman *et al.*, 2019). These advantages are promising to human health, especially in deciphering the issue of antibiotic resistance by pathogens.

Relationship of endophytic fungi and novel bioactive compounds

According to Yu *et al.* (2010), most of the fungi are isolated from medicinal plants (35%), followed by crops (29%), plants in special environments (18%) and other plants (18%) (Figure 1). It is noteworthy to mention that numerous endophytes are capable to mock similar compounds with their host plants. The relationship of endophytic fungi and their host plant is based on a unique adaptation. Through this condition, fungi could synchronize their growth with the host plant (Verma *et al.*, 2012). Other than commensal association or neutralism, endophytes can survive on their host *via* parasitic and mutualistic relationships (Gouda *et al.*, 2016).

The relationship depends on the genotype of the endophyte and the host plant itself. Besides that, the environmental condition is also an important key in selecting the relationship (Faeth & Fagan, 2002). However, most endophytic fungi are mutualists since they gain nutrition and protection from the host plant. As a return, they offer an extra competitive ability and resistance against plant-eating animals, insects, pathogens, and abiotic stresses (Oukala *et al.*, 2021). To protect the synergistic relationship with the host plant, the endophytic fungi confer three beneficial offers; (1) producing growth hormones to the host (Waqas *et al.*, 2012), (2) increasing the host resistance to biotic and abiotic stresses by generating specific bioactive compounds (Rodriguez *et al.*, 2009), and (3) endorsing the accretion of secondary metabolites such as medicinal drugs (Shwab & Keller, 2008). Most of the endophytic fungi are antimicrobial agents. In Asian medicinal plants, they represent 46% of the total findings (Figure 2). The endophytic fungi are also actively reported to be an agent for anticancer, anti-inflammatory, antioxidant, antidiabetic, and other biological activities. According to this persuasive potential, it is well worth exploring and investigating the novel endophytic fungi, which might offer a better option in treating human diseases.

Endophytic fungi as an antimicrobial agent

Several novel antibiotics that are medically potent can be isolated from endophytic fungi (Strobel & Daisy, 2003). Many new antimicrobial compounds were isolated from *Phomopsis* and its anamorph *Diaporthe*. Four pyrenosines, known as phomopsinone A, B, C, and D were discovered from *Phomopsis* sp., which resided in the stems of *Santolina chamaecyparissus* (Hussain *et al.*, 2012a). It has been reported that *Botrytis cinerea*, *Pyricularia oryzae*, and *Septoria tritici* were vulnerable to phomopsinone A. The antimicrobial activity of phomopsinone A was represented by the highest inhibition zones ranged from 17-25 mm. Meanwhile, phomopsinone B manifested moderate antifungal and antibacterial activities, particularly against *P. oryzae*, *Microbotyrum violaceum*, *S. tritici*, *Escherichia coli* and *Bacillus megaterium*. Phomopsinone C also showed moderate inhibitory activities against *M. violaceum*, *E. coli*, and *B. megaterium*, while phomopsinone D

moderately inhibited fungi *Botrytis cinerea* and *S. tritici*. The inhibition zones caused by these drugs were specifically ≤ 10 mm. Another 4 pyrenosines, namely pyrenosines J, K, L and M were isolated from *Phomopsis* sp. residing in *Cistus salvifolius* (internal strain 7852) by the same group of the researcher. All the compounds exhibited antibacterial properties on *E. coli* and, *B. megaterium*, however only pyrenosines J, K, and, M showed antifungal properties against *S. tritici* and, *M. violaceum* (Hussain *et al.*, 2012b). Later Sun *et al.* (2013a) have discovered four types of hydroxyanthraquinones, together with four new analogs (coniothyronones A-D) containing tetralone moiety from endophytic fungus *Coniothyrium* sp. This fungus was found on *Salsola*

oppositifolia plant. All compounds showed antibacterial activity against *B. megaterium*. The radius of inhibition zone was ranged from 7-16 mm. The compounds have also signified moderate biological activity on *E. coli*, except hydroxyanthraquinones 1. Interestingly, Tong *et al.* (2017) have discovered a novel ketone derivative, 3-hydroxy-5-methoxyhex-5-ene-2,4-dione, from *Diaporthe* sp. ED2, which was isolated from medicinal plant *Orthosiphon stamineus*. The heat-stable compound exhibited significant fungicidal activity on *Candida albicans* at MIC and minimal fungicidal concentration (MFC) of 3.1 $\mu\text{g/mL}$ and 12.5 $\mu\text{g/mL}$, respectively. The test compound has reduced 99.9% of viable cell count after 36 h of exposure to *C. albicans*.

Figure 1. Percentage of endophytic fungi from different host sources (adapted from Yu *et al.*, 2010).

Figure 2. Biological activities of various endophytes isolated from medicinal plants in Asia (adapted from Sharma *et al.*, 2020).

Marine and mangrove ecosystems are commonly known as great reservoirs for novel antimicrobial compounds. Sebastianes *et al.* (2012) has reported the production of 3-hydroxypropionic acid (3-HPA) from an endophytic fungus, *Phomopsis phaseolorum*. This fungus was isolated from mangrove's branches of *Laguncularia racemosa*. 3-HPA showed the antibacterial effect on *Staphylococcus aureus* and *Salmonella typhi*, with minimal inhibitory concentration (MIC) of 64 µg/mL. However, the value was less compelling than tetracycline. Pestalotiopen A was firstly isolated from *Pestalotiopsis* sp., which resided on a Chinese mangrove *Rhizophora mucronata*. It is suggested that cyclopaldic acid and altioxin B become co-occurring precursors during the biosynthesis of pestalotiopen A. The compound revealed moderate antibacterial efficiency on *Enterococcus faecalis*, with MIC values ranged from 125-250 mg/mL (Hemberger *et al.*, 2013). Cristatumin A and tardioxopiperazine A is an indole alkaloid extracted from *Eurotium cristatum* sp. EN-220 from *Sargassum thunbergii*. The compound inhibited both *E. coli* and *S. aureus* at MIC values of 64 µg/mL and 8 µg/mL, respectively (Du *et al.*, 2012). Other metabolites, which are named as isorhodoptilometrin-1-methyl ether and siderin, have shown antibacterial activity against indicator strains of *B. cereus*, *B. subtilis* and *S. aureus*. Against these bacteria, siderin slightly emerged a better antibacterial activity than isorhodoptilometrin-1-methyl ether, with a radius of inhibition zone ranged from 12-15 mm. Both compounds were isolated from *Aspergillus versicolor*, which was initially from red sea algae (Hawas *et al.*, 2012). Two novel antimicrobial compounds of xanthone derivatives, namely yicathin B and C were discovered from endophyte *Aspergillus wentii* PT-1 of *Gymnogongrus flabelliformis*, the red marine alga originated from Pingtan Island, China. Yicathin B could potentially inhibit *E. coli*, with 9 mm inhibition zone. Meanwhile, yicathin C has a broader spectrum of the antimicrobial activity than yicathin B. It was active against bacteria and fungus that of *E. coli*, *S. aureus* and *Colletotrichum lagenarium*, with 12 mm, 7.5 mm and 11 mm inhibition zones, respectively (Sun *et al.*, 2013b). The sub-toxicity values for both compounds were 0.22 mmol/L (Yicathin B) and 0.30 mmol/mL (Yicathin C). It is also noteworthy to report a

newly discovered antibacterial compound that originated from marine-derived *Aspergillus flavipes*. The compound is aromatic butyrolactone, which is known as Flavipesins A. It functioned as a potent antibacterial agent against *S. aureus* (MIC = 8 µg/mL) and *B. subtilis* (MIC = 0.25 µg/mL). This compound penetrated *via* the biofilm matrix of the matured *S. aureus* and killed the available free-living cells in the biofilm (Bai *et al.*, 2015). A novel ketone derivative (3,1'-didehydro-3[2''(3''',3'''-dimethyl-prop-2-enyl)-3''-indolylmethylene]-6-methyl piperazine-2,5-dione) was isolated from *Penicillium chrysogenum* MTCC 5108. This fungus mutually resided on the leaves of the mangrove plant *Porteresia coarctata* (Roxb.). The antibacterial activity of the identified compound was relative to commercial streptomycin. Both drugs displayed a comparable range of inhibition zone, that of 14-16 mm, against *Vibrio cholerae* (Devi *et al.*, 2012). Huang *et al.* (2017) reported a new anthraquinone derivative from mangrove endophyte *Phoma* sp., isolated from *Myoporum bontiodendron* A roots, which is called 7-methoxymacrosporin. By comparing with the positive control carbendazim, 7-methoxymacrosporin owned a potent antifungal activity on *Fusarium oxysporum* with MIC value equal to 3.75 µg/mL.

Pyrrocidine C was first recovered from *Levia infectoria* SNB-GTC2402, an endophytic fungus found in the tropical leaf, *Besleria insolita*. The compound has an antibacterial efficiency against Gram-positive *S. aureus* ATCC 29213, with MIC equivalent to 2 µg/mL (Casella *et al.*, 2013). Cheng *et al.* (2012) have reported that higher MIC values, that of 5.12 mg/mL and 2.52 mg/mL, were needed by biscogniazaphilones A and B to inhibit *Mycobacterium tuberculosis*. These two novel antimycobacterial azaphilone derivatives were discovered from *Biscogniauxia formosana* BCRC 33718, which was originally from the bark of a *Cinnamomum* sp. A new phenolic chemical, 4-(2,4,7-trioxa-bicyclo [4.1.0]heptan-3-yl)-phenol was previously isolated from *Pestalotiopsis mangifera*, a fungus isolated from the mango tree. The compound manifested significant inhibitory activity on both Gram-positive and Gram-negative bacteria as well as yeast. The MIC values were ranged from 0.039 to 5.0 µg/mL, with the lowest value recorded by *B. subtilis*, *K. pneumoniae* and *C. albicans*. According to the microscopic

evaluation, this compound destroyed bacterial cells through cytoplasm cohesion (Subban *et al.*, 2013).

Budhiraja *et al.* (2013) discovered another new chemical, KL-4 or 6-methyl-1,2,3-trihydroxy-7,8-cyclohepta-9,12-diene-11-one-5,6,7,8-tetralene-7-acetamide. It was from *Aspergillus* sp., which was previously isolated from the seeds of medicinal plant *Gloriosa superba* Linn. The identified compound displayed an excellent antimicrobial activity on *S. aureus*, *E. coli*, *Saccharomyces cerevisiae*, *C. albicans*, *P. aeruginosa*, *B. subtilis*, and *Cryptococcus gastricus*. The susceptibility of these microbes on the test compound was signified by the inhibition zone, with an average diameter from 11.9 to 18.9 mm. Moreover, several novel polyketides were also discovered from endophytic fungi including 7,8-dihydronivefuranone A, 6(7)-dehydro-8-hydroxyterrefuranone, 6-hydroxyterrefuranone and nivefuranones A. These compounds were isolated from *Microdiplodia* sp. KS 75-1, an endophytic fungus inhabiting in the stems of *Pinus* sp. Against *C. albicans* and *S. aureus*, the newly purified compounds manifested a compelling range of inhibition zones on both microbes *viz.* 15-16 mm (*S. aureus*) and 13-15 mm (*C. albicans*) (Shiono *et al.*, 2012). Saleem *et al.* (2013) have reported the antibacterial efficacy of cryptosporioptide. This polyketide can inhibit the growth of *B. megaterium*. It was extracted and isolated from *Cryptosporiopsis* sp., which was originally from the shoot tissue of *Viburnum tinus*. Based on agar diffusion test, this compound has moderately inhibited *B. megaterium* with a 9 mm diameter of inhibition zone. This zone was smaller than positive control penicillin (26 mm) and streptomycin (13 mm). Senadeera *et al.* (2012) have reported a potentially antibacterial polyketide compound, that of dothideomycetide A, against *S. aureus* ATCC 25923 and methicillin resistant *S. aureus* ATCC 33591. It was isolated from *Dothideomycete* sp., which was originally from the Thai medicinal plant *Tiliacora triandra*. This compound presented antibacterial activity on *S. aureus* and MRSA with corresponding MIC values of 128 and 256 µg/mL.

Endophytic fungal products as anticancer agents

Cancer has become one of the most leading causes of death worldwide, which approximately

10 million people died from this disease in 2020. The number of cases is estimated to increase by 47% in 2040, accounting for 28.4 million cases (Sung *et al.*, 2021). Among cancer diseases, lung cancer is the major killer in humans. It has represented 18.4% of total cases. Besides, lung cancer is recognized as the most diagnosed disease alongside breast cancer (11.6%). It is closely tailed by prostate cancer (7.1%), colorectal cancer (6.1%), stomach cancer (8.2%), and liver cancer (8.2%) (Bray *et al.*, 2018). There are several actives from endophytic fungi, which scientists believed can be an optional drug against cancerous cells. The potential actives are discussed in this section.

Paclitaxel

Paclitaxel, or commercially known as taxol was discovered in 1960 from a screening program of antitumor activity held by National Cancer Institute (Weaver, 2014). It is the world's first billion-dollar project using fungi as an anticancer agent, though the drug is primarily isolated from the bark of *Taxus brevifolia*. Large-scale production of the compound has caused a delay on the clinical development of taxol (El-Sayed *et al.*, 2020). Researchers have acknowledged *Taxus* sp. (yew) as a key of interest due to their potential in producing taxol. It has been stated that taxol produced by *Taxus* sp. could be the chemical that protects the yew tree since this plant is lethal to numerous pathogenic oomycetes including *Phytophthora* sp., *Pythium* sp. and *Aphanomyces* sp. The mystery is solved with the finding of fungus *Taxomyces adreanea* in *T. brevifolia* as a paclitaxel producer. A detection *via* electrospray mass spectrum using culture fluid of this fungus has confirmed the presence of paclitaxel. There were two peaks observed i.e. (M + H⁺) and (M + Na⁺) at *m/z* 854 and *m/z* 876, respectively. The peaks are identical with authentic taxol (molecular formula: C₄₇H₅₁NO₁₄) (Strobel *et al.*, 1997). Moreover, the investigations relate to the ¹⁴C-label unquestionably demonstrated the existence of taxol-derived fungus in the culture medium. In 1996, Strobel and co-researchers have isolated paclitaxel from an endophytic fungus, *Pestalotiopsis microspore*, which originally from inner bark of Himalayan yew, *Taxus wallichiana*. They found out that [¹⁴C]acetate and [¹⁴C]phenylalanine are served as precursors for [¹⁴C]taxol in fungal

culture labeling analyses. Xiao *et al.* (2012) have confirmed that this ¹⁴C-label could increase uptake by tumor tissue and slow down pharmacokinetics on cancerous mice models. It is worth to mention a more recent discovery of taxol producing endophytic fungi such as *Tubercularia sp.* It was isolated from Chinese yew or *Taxus mairei* (Wang *et al.*, 2000). Based on the immunofluorescence result, this fungal taxol has altered the intracellular microtubule arrays, which relative to commercial taxol. This event has allowed mitotic arrest and cytotoxicity on cancerous cells. Other than ¹⁴C-label, taxol can also be detected according to the BAPT gene (C-13 phenylpropanoid side chain-CoA acetyltransferase). Garyali *et al.* (2013) have discovered this method during the taxol identification produced by *Fusarium redolens*. The BAPT gene is reported to associate with the taxol biosynthetic pathways. However, the production was low as only 66 µg/L of taxol generated in fermentation broth.

In 2011, *Colletotrichum capsici* was isolated from the infected fruits of chili plant *Capsicum annum*, which was later identified as taxol-producing fungus. The highest amount of fungal taxol production was 687 mg/L, with a production rate of 13740-fold (Kumaran *et al.*, 2011). Another taxol producer was *Seimatoantlerium tepuiense*. It was isolated from *Maguireothamnus speciosus*, a widespread plant which commonly can be found on the table-top mountain of the Venezuelan-Guyana region in southwestern Venezuela (Zhang & Demain, 2005). These reports have proven that the distribution of taxol producing endophytic fungi in plants are varied and not only limited to yews. The worldwide distribution of the fungi is related to the fungicidal characteristic of taxol. As recorded, *Pythium sp.* and *Phytophthora sp.* are the most sensitive plant pathogens on taxol (Young *et al.*, 1992).

The existence of a trace number of unattached kinetochores in taxol has become a hallmark cytotoxic property against human cervical cancer cells (HeLa). At nanomolar concentrations, this compound can arrest cells which is available at the mitotic (M) phase of the cell, without interruption of the synthesis (S) phase (Waters *et al.*, 1998). Besides, this compound owns the ability to improve the polymerization of stable microtubules (Wani and Horwitz, 2014). The

result was in line with the previous findings as taxol could stabilize the microtubules by promoting the polymerization process and at the same time obstructing the depolymerization. According to this exceptional mode of action, taxol is acknowledged as the latest class of antineoplastic agents (Schiff *et al.*, 1979; Horwitz *et al.*, 1986). By inducing the activation of the mitotic checkpoint, taxol provides a pause in the division of chromosomes entering mitosis as copied pairs of sister chromatids. This process continued until each pair has formed secure adhesions to both mitotic spindle poles. Therefore, each cell will obtain one replicate of every chromatid. The chromatids link to spindle microtubules *via* kinetochores, which are a cluster of protein structures that build on centromere parts of DNA. Free kinetochores which formed fragile attachments to microtubules have alternately initiated a signal transduction cascade to slow down mitotic progression. This process has been done by averting the anaphase endorsing complex or cyclosome (Foley & Kapoor, 2013).

Camptothecin

In 1966, Wall and Wani isolated a potential antitumor agent from *Camptotheca acuminata*, which is known as camptothecin (CPT). It is a type of pentacyclic pyrroloquinoline alkaloid that stabilizes the reversible covalent DNA-topoisomerase I complex. Topoisomerase I relax DNA by breaking it, prior to resealing step of a single strand of DNA. Consequently, it discharges the torsional strain that ensues through DNA transcription and replication (Chu *et al.*, 2014). It has been reported that CPT derivatives comprised the anticancer activity of both *in vitro* and *in vivo*. The parental compound of 10-hydroxycamptothecin, topotecan (IPT), irinotecan (CPT-I 1), and SN-38 is alkaloid CPT (Thomas *et al.*, 2004). Previous reports claimed that CPT is naturally produced by several other plant species including *Camptotheca acuminata* Decaisne (Nyssaceae) and *Nothapodytes foetida* (Padmanabha *et al.*, 2006; Pu *et al.*, 2013). The high request for CPT has been rooted in the mass harvesting of these two plants in recent years. As an alternate strategy, researchers have put a weight on the habitant of the plants or endophytic microorganisms in finding a new CPT source.

In the recent past, the first report of CPT-producing endophytic fungus, specifically *Entrophospora infrequens*, was discovered by Puri *et al.* (2005). This fungus was isolated from the inner bark of *Nothapodytes foetida*. The fungus was grown in a shake flask and bench-scale system containing a synthetic submerged medium (Sabouraud broth). The fermentation process has allowed the fungus to synthesize the similar anticancer compound or CPT generated by the host tree itself. This finding encourages a more wide-ranging search of other plants. The interest in investigating other endophytic sources of CPT and its derivatives from different plant sources has certainly been revived by these interesting findings. Rehman *et al.* (2008) reported a potential source of CPT from endophytes of *N. foetida* seed. It has been recorded by Min and Wang (2009) that there was an anonymous endophytic fungal strain XK001 from *C. acuminata* could generate 10-OH-CPT. Furthermore, CPT and its analogs specifically 9-methoxy camptothecine (9-MeO-CPT) and 10-OH-CPT were successfully isolated from endophytic fungi. The fungi were originally from *C. acuminata* and *Apodytes dimidiata* (Icacinaeae) (Kusari *et al.*, 2009; Shweta *et al.*, 2010). Based on Chu *et al.* (2014), CPTs signified an essential class of anticancer drugs. Their capabilities in inhibiting several solid tumors such as lymphoma, gastric cancer as well as colorectal cancer have been widely reported by researchers.

Vinblastine and vincristine

Vinblastine and vincristine, which are isolated from the leaves of *Catharanthus roseus*, are excellent anti-cancer medicines. It is a short-lived perennial that belongs to the family of Apocynaceae and contains more than one hundred medicinal terpenoid indole alkaloids, including the two main vinca alkaloids, vincristine and vinblastine (Palem *et al.*, 2015). The mechanisms of action of vincristine are represented with the intrusion of microtubule development and mitotic spindle dynamics. In addition, it causes a disturbance of intracellular transport and also able to reduce tumor blood flow. Vincristine is isolated from *Fusarium oxysporum*, an endophyte of *C. roseus* (Zhang *et al.*, 2000; Tung *et al.*, 2002). This compound has been produced by *Alternaria* sp., which is isolated from the same plant found in China (Guo & Kunming, 1998). Kumar *et al.*

(2013) have reported on the isolation of fungus AA-CRL-6 from *C. roseus*, which could generate vinblastine and vincristine. This fungus was distinguished according to its cultural and morphological characteristics as well as molecular approach *via* internal transcribed spacer (ITS) sequence evaluation. It was identified as *F. oxysporum*. Palem *et al.* (2015) have reported their work on vincristine and vinblastine-producing fungus, *Talaromyces radicus* which also been isolated from *C. roseus*.

Podophyllotoxin

Podophyllotoxin (PDT) is a well-known natural aryl tetralin lignan produced by a few plant species. Commonly, it is implemented to be a precursor in some chemical synthesis which involved anticancer drugs such as etoposide, teniposide and etopophosphate phosphate (Nadeem *et al.*, 2012). To date, sinopodophyllum is the main plant reservoir for podophyllotoxin. Sinopodophyllum plants have been declared imperiled as over-exploitation species due to the mass harvest. An alternative resource and strategy for producing this important compound effectively should be developed in order to meet the growing demand. Yang and co-researchers have identified about six endophytic fungi that could produce PDT particularly from *Sinopodophyllum hexandrum*, *Diphylleia sinensis* and *Dysosma veitchii* (Yang *et al.*, 2003). Subsequently, Lu *et al.* (2006) have also stated that PDT could be generated from an endophytic *Alternaria* sp., which was previously obtained from *Sabina vulgaris*. Two endophytic strains of *Phialocephala fortinii*, specifically PPE5 and PPE7, could produce PDT in submerged suspension culture. The fungi were isolated from *Sinopodophyllum peltatum* and generated about 0.5 to 189 µg/L in yield (Eyberger *et al.*, 2006). Puri and co-researchers have also reported PDT and its glycoside in broth culture which was initially isolated from an endophytic fungus *Trametes hirsute*. This fungus was purified from *Sinopodophyllum hexandrum* (Puri *et al.*, 2006). Cao *et al.* (2007) have confirmed that an endophytic fungus, specifically *Alternaria* sp., which isolated from *S. hexandrum* could generate PDT. Kour and co-researchers have also recognized a PDT-generating endophytic fungus *F. oxysporum* attained from *Sabina recurva* in 2008 (Kour *et al.*,

2008). The latest report by Nadeem *et al.* (2012) showed the synthesis of PDT by an endophytic fungus *Fusarium solani* isolated from the roots of *Podophyllum hexandrum*. HPLC and mass spectrometry have confirmed and quantified the existence of PDT in fungal biomass. These findings provide us with a promising way to explore endophytic fungi as an optional source for PDT and its analogs.

Other anticancer agents

A later report by Tawfike *et al.* (2019) have revealed seven actives isolated from *A. flocculus*. However, only five actives, specifically *cis*-4-hydroxymellein, 5-hydroxymellein, diorcinol, botryoisocoumarin A and mellein, exhibited an anticancer effect on the formation of a chronic myelogenous leukemia cell line. Majoumouo *et al.* (2020) have disclosed the cytotoxicity prospective of *Trichoderma* sp. extract against human cervical cancer cells. This endophytic fungus was previously isolated from *Terminalia catappa*. The N97 extract owned a notable anticancer effect on human cervical cancer cells with a 50% inhibitory concentration (IC₅₀) equal to 33.35 µg/mL. A higher IC₅₀ value was exhibited by other tested extracts including N223 (136.8 µg/mL), N169 (149.2 µg/mL) and N2 (175.8 µg/mL). In addition, it was verified that the growth inhibitory potential of the *Trichoderma* sp. extract on cancer cells was intervened *via* apoptosis during the application of N97 extract. Chemical structures of important anticancer agents are displayed in Figure 3.

Endophytic fungal products as antioxidant agents

The antioxidant is referred to any constituent that interrupts, stops, or eradicates oxidative defect to a target molecule. Endophytes are a perfect source of compounds with antioxidants. Two compounds, specifically terreic acid and 6-methylsalicylic acid, were obtained from *Pseudocercospora* sp. ESL 02, an endophytic fungus isolated from a plant called *Elaeocarpus sylvestris*.

Both compounds have displayed a promising result on DPPH radical scavenging activity, mitigating power assay and β-carotene bleaching assay (Prihantin & Tachibana, 2017). In a previous report, terreic acid is a bioactive compound, which commonly derived from 6-methylsalicylic acid (6-MSA) (Guo *et al.*, 2014). The ability of terreic acid to scavenge toward free radicals is based on its quinine group which serves a major role in bringing a balance between antioxidants and reactive oxygen species generated within the system. Moreover, the potential of this compound as an antioxidant agent was supported by Dewi *et al.* (2012). They have validated that terreic acid isolated from ethyl acetate extract of *Aspergillus terreus* LS01 displayed a moderate radical scavenging activity. Furthermore, *Aspergillus* genera are extensively described to produce numerous secondary metabolites such as wentiquinone C, methyl 4-(3,4-dihydroxybenzamido)butanoate (Li *et al.*, 2014) and exopolysaccharide As1-1 (Chen *et al.*, 2011). After several years of effort, it has been reported that two compounds, specifically pestacin and isopestacin, are produced by *P. microspore*. This endophytic fungus was discovered by Harper *et al.* (2003) from *Terminalia morobensis* plant. Both pestacin and isopestacin possess a potent antioxidant activity which relative to the flavonoids. Graphislactone A, a metabolite purified from an endophytic *Cephalosporium* sp., displayed an antioxidant activity as well as free radical scavenging. The *in vitro* assessment of the compound showed stronger antioxidant activity than butylated hydroxytoluene (BHT) and ascorbic acid. During radical scavenging activity test, Graphislactone A has manifested a lower IC₅₀ value than BHT *viz.* 9.6 µM and 19.5 µM, respectively. As for ascorbic acid, a dire elevation in linoleic acid peroxidation was observed after 30 h, with OD_{500nm} more than 0.6. The condition was equivalent to that of the blank. On the other hand, Graphislactone A has recorded a 4.4-fold decrease of linoleic acid peroxidation at a similar experimental period (Song *et al.*, 2005).

Figure 3. Structures of bioactive compounds with anticancer efficiency isolated from different endophytic fungi (adapted from Strobel *et al.*, 2003; Eyberger *et al.*, 2006; Shweta *et al.*, 2010; Kumar *et al.*, 2013; Tawfike *et al.*, 2019).

Antidiabetic agent

Medically, diabetes insinuates a cluster of metabolic diseases described by conditions with high blood glucose concentration (hyperglycemia) linked to insufficient insulin production or the body's cells failed to respond properly to insulin, or both (Ushasri & Anusha, 2015). It is one of the most common diseases that causes serious public health concerns as there are limited drugs available for treatment. Thus, many investigations are focused on novel antidiabetic drugs from

endophytic fungi (Dhankhar *et al.*, 2013; Prabavathy & Vallinachiyar, 2013; Singh & Kaur, 2016). A purified peptide molecule from *Aspergillus awamori* isolated from *Acacia nilotica* has showed antidiabetic activity. The compound obtained from the study has dual inhibitory activity, particularly α -glucosidase (80%) and α -amylase (81%). Furthermore, it has low IC₅₀ values (α -glucosidase = 5.625 μ g/mL; α -amylase = 3.75 μ g/mL) and stable at high temperature and pH. The peptide retained 80% of inhibitory

activity after 1 h exposure to a temperature of 80°C. By virtue of these characteristics, this compound can be commercially produced (Singh & Kaur, 2016). Zhang *et al.* (1999) have reported a different antidiabetic compound. It is a nonpeptide fungal metabolite *viz.* demethylasterriquinone B1, which was isolated from the endophytic fungus, *Pseudomassaria* sp. Originally, it was collected from an African rainforest in Congo. This compound showed a significant result of lowering blood glucose levels in the mouse model. The similar outcome was reported during the application of N-acetylgalactosamine (lectin) on alloxan-induced diabetic rats. This antidiabetic agent was isolated from *Alternaria* species, an endophyte of the plant *Viscum album*. It has inhibited three diabetic components, particularly α -amylase, α -glucosidase and sucrase. Interestingly, the compound displayed an increase in mice body weight by 8.5% after 14 days of experimental period (Govindappa *et al.*, 2015).

Immunosuppressive agent

Immunosuppression is the process that acts to decrease the activation or efficacy of the immune system by cell-mediated immunity. Immunosuppressive agents are molecules that inhibit or prevent the activity of the immune system involved in autoimmune diseases or organ transplants. A sample of plant materials of *Pteromischum* sp. collected from a rainforest in Costa Rica was found an endophytic fungus, *Colletotrichum dematium* which strongly inhibited *Botrytis cinerea*, a typical plant pathogen on the leaves and flowers. The fungus *C. dematium* produced a molecule, Colutellin A, which chemically and biologically resemblances to cyclosporin A, an important immunosuppressive drug (Rüegger *et al.*, 1976).

Immunosuppressive drugs, such as Subglutinol A and Subglutinol B, were used to avert transplant rejection in patients. The drugs were produced by *Fusarium subglutinans*, an endophytic fungus from the perennial twining-type vine *Tripterygium wilfordii*. Both Subglutinol A and Subglutinol B were discovered to be equipotent with IC₅₀ of 0.1 μ M in the thymocyte proliferation assay and lymphocyte reaction assay (Lee *et al.*, 1995). Chloroform and methanolic extracts of endophytic fungus *Entrophospora*

infrequens isolated from *N. foetida* have exhibited immunomodulatory potential in mice models. At a concentration range of 12.5-100 mg/kg body weight, the chloroform extract has accelerated the humoral and cell-mediated immune responses in a dose-dependent pattern. As for the methanolic extract, it induced the delayed-type hypersensitivity (DTH), plaque-forming cell assay, phagocytic response, haemagglutination antibody titer and immunoglobulin G by 80%, 33%, 38%, 79.07% and 62.05%, respectively. These occasions happened at a concentration of 12.5 mg/kg body weight (Puri *et al.*, 2007). It is also notable to expose a compound, which was known as BS compound. The compound was isolated from the fungus, *Pestalotiopsis leucothes*, an endophytic fungus of the plant *Tripterygium wilfordii*. It showed immunomodulatory activity with IC₅₀ value ≤ 0.35 during the proliferative assays. Additionally, this compound has a variable impact on T cells, B cells and monocytes (Kumar *et al.*, 2005).

Anti-arthritis and anti-inflammatory activities

Arthritis is the inflammation of tissues in the joints with chronic systemic autoimmune disease, characterized by pain, swelling, and obliteration of cartilage and bone which leading to permanent disabilities. Currently, researchers are drawing a great interest to expedite the search of biomolecules from endophytic fungi associated with medicinal plants due to certain side effects of the available drugs (Choudhary *et al.*, 2015). An endophytic fungal screening program is crucial in finding an inhibitor for pro-inflammatory cytokines. Molecules from endophytic fungal *Talaromyces wortmannii*, which was isolated from *Aloe vera*, showed potent anti-inflammatory activity. The result exhibited that retardation of IL-8 release was executed by obstructing the NF- κ B and AP-1 activation (Pretsch *et al.*, 2014). Simultaneously, mutolide isolated from the fungus *Lepidosphaeria* sp. has also disclosed an exceptional anti-inflammatory activity. At 100 mg/kg body weight, mutolide manifested notable inhibition of lipopolysaccharide (LPS)-induced release of tumor necrosis factor-alpha and interleukin 6 from acute inflammation mice models. It blocked both pro-inflammatory cytokines, with an IC₅₀ equivalent to 1.27 ± 0.06 and 1.07 ± 0.02 μ M, correspondingly. As

observed, the process did not affect the viability of the cells. This compound is a better candidate for treating inflammatory diseases like rheumatoid arthritis (Shah *et al.*, 2015).

Anti cholesterolemic agent

Mortality caused by cardiovascular diseases (CVDs) has manifested approximately 17.5 million cases in 2012 and is expected to project a gradual rise to 22.2 million cases by 2030 (Patel *et al.*, 2011). Based on a report by Praveen and co-authors, the endophytic fungi are a poor candidate to produce lovastatin compared to the fungi from soil isolate (Praveen *et al.*, 2014). However, this claim has been denied by Ahmed El-Gendy *et al.* (2016), Patil *et al.* (2017) and Kanjana *et al.* (2019). Lovastatin is a natural statin drug used in CVDs treatment after the compactin failure (Endo, 2010). In general, statins inhibit 3-hydroxy-3-methylglutaryl CoA or HMG-CoA reductase in the cholesterol biosynthesis pathway. Statins are the premium prescribed drug to cholesterolemia patients, albeit some of the statins are associated with adverse effects. Patients are commonly suffering from statins intolerance (Arca *et al.*, 2012) or, even worst, the development of atherosclerosis. This event is triggered accordingly by the increase of low-density lipoprotein (LDL), specifically oxidized LDL, which later commences monocyte adhesion and eventually driving to atherosclerotic occasions. Thus, it is crucial to avert LDL oxidization (Patil *et al.*, 2017). Bioactive compounds originated from phenolics are known for their antioxidant and anti-inflammatory activity, which represent an excellent potential against CVDs (Deng & Chow, 2010). The phenolics of natural origin are able to decline the oxidation of lipids, as well as proteins (Ellingsen *et al.*, 2009). Besides, the phenolics also own redox properties and capability in quenching reactive oxygen (Patil *et al.*, 2017). These biological actions are appropriate to protect the human body from arterial stiffening and atherosclerosis. *Phyllosticta spinarum* (Wijeratne *et al.*, 2008), *Aspergillus luchuensis* (Ahmed El-Gendy *et al.*, 2016), *Diaporthe arengae* (Patil *et al.*, 2017),

Chaetomium globosum, *Cladosporium tenuissimum* and *Penicillium janthinellum* (Kanjana *et al.*, 2019) are amongst the endophytic fungi that could reduce the *in vitro* and *in vivo* cholesterolemia event. From cypress a coniferous tree or *Platycladus orientalis*, Wijetrane *et al.* (2008) has isolated *P. spinarum*. This endophytic fungus owns tauranin, a sesquiterpene quinone, which functions to inhibit the assimilation of acetate-1-14C into free and esterified cholesterol.

Ahmed El-Gendy *et al.* (2016) have suggested gene transfer *via* genome shuffling technique to boost lovastatin production by using marine mangrove endophytic fungus, *A. luchuensis* MERV10. The strain improvement scheme, associated with solid-state fermentation system, has multiplied 32-fold of lovastatin productivity which was 2.11 times higher than the parental culture. According to Patil *et al.* (2017), *D. arengae* is another prospective anti-hypercholesterolemic fungus resides in the twig tissue of *Terminalia arjuna*. It is rich in phenolic compounds such as benzene propionic acid, 3,5-bis (1,1-dimethylethyl)-4-hydroxy methyl ester, pterin-6-carboxylic acid and 2,6-ditert-butyl-4-phenol. In general, the *in vivo* study on albino Wistar rats has denoted the cholesterol results displayed by fractionated *D. arengae* extract were relative to standard atorvastatin. It is also worth to mention a work by Kanjana *et al.* (2019) on three endophytic fungi, specifically *C. globosum*, *C. tenuissimum* and *P. janthinellum*. These fungi were isolated from therapeutic plants i.e., *Passiflora foetida*, *Memecylon edule* and *Justicia adhatoda*, respectively. There are several potential anti cholesterolemic agent available in the ethyl acetate extract, including benzene propionic acid, 3,5-bis (1,1-dimethylethyl)-4-hydroxy methyl ester, pterin-6-carboxylic acid, 2,6-ditert-butyl-4-phenol, (Z,Z)-9,12-octadecadienoic acid, n-hexadecanoic acid, acetic acid, cinnamyl ester, hexadecanoic acid, methyl ester and tetradecanoic acid. Series of endophytic fungi with their novel compounds, biological activities and original host plants are summarized in Table 1.

Table 1. Series of novel bioactive compounds with different biological activities isolated from various endophytic fungi.

Actives	Types of Fungi	Host	Activity	References
Pyrenosines (phomopsinone A, B, C and D)	<i>Phomopsis</i> sp.	Stems of <i>Santolina chamaecyparissus</i>	Antimicrobial	Hussain <i>et al.</i> (2012a)
Pyrenosines J, K L and M	<i>Phomopsis</i> sp.	<i>Cistus salvifolius</i>	Antimicrobial	Hussain <i>et al.</i> (2012b)
Hydroxyanthraquinones 1	<i>Coniothyrium</i> sp.	<i>Salsola oppositifolia</i>	Antimicrobial	Sun <i>et al.</i> (2013a)
Hydroxyanthraquinones 2	<i>Coniothyrium</i> sp.	<i>Salsola oppositifolia</i>	Antimicrobial	Sun <i>et al.</i> (2013a)
Hydroxyanthraquinones 3	<i>Coniothyrium</i> sp.	<i>Salsola oppositifolia</i>	Antimicrobial	Sun <i>et al.</i> (2013a)
Hydroxyanthraquinones 4	<i>Coniothyrium</i> sp.	<i>Salsola oppositifolia</i>	Antimicrobial	Sun <i>et al.</i> (2013a)
Coniothyronones A	<i>Coniothyrium</i> sp.	<i>Salsola oppositifolia</i>	Antimicrobial	Sun <i>et al.</i> (2013a)
Coniothyronones B	<i>Coniothyrium</i> sp.	<i>Salsola oppositifolia</i>	Antimicrobial	Sun <i>et al.</i> (2013a)
Coniothyronones C	<i>Coniothyrium</i> sp.	<i>Salsola oppositifolia</i>	Antimicrobial	Sun <i>et al.</i> (2013a)
Coniothyronones D	<i>Coniothyrium</i> sp.	<i>Salsola oppositifolia</i>	Antimicrobial	Sun <i>et al.</i> (2013a)
3-hydroxy-5-methoxyhex-5-ene-2,4-dione	<i>Diaporthe</i> sp. ED2	<i>Orthosiphon stamineus</i>	Antimicrobial	Tong <i>et al.</i> (2017)
3-hydroxypropionic acid	<i>Phomopsis phaseolorum</i>	Branches of mangrove <i>Laguncularia racemosa</i>	Antimicrobial	Sebastianes <i>et al.</i> (2012)
Pestalotiopen A	<i>Pestalotiopsis</i> sp.	Chinese mangrove <i>Rhizophora mucronata</i>	Antimicrobial	Hemberger <i>et al.</i> (2013)
Cristatumin A	<i>Eurotium cristatum</i> sp. EN-220	Marine alga <i>Sargassum thunbergii</i>	Antimicrobial	Du <i>et al.</i> (2012)
Tardioxopiperazine A	<i>Eurotium cristatum</i> sp. EN-220	Marine alga <i>Sargassum thunbergii</i>	Antimicrobial	Du <i>et al.</i> (2012)
Isorhodoptilometrin-1-methyl ether	<i>Aspergillus versicolor</i>	Green alga <i>Halimeda opuntia</i> internal tissues	Antimicrobial	Hawas <i>et al.</i> (2012)
Siderin	<i>Aspergillus versicolor</i>	Green alga <i>Halimeda opuntia</i> internal tissues	Antimicrobial	Hawas <i>et al.</i> (2012)
Yicathin B	<i>Aspergillus wentii</i> PT- 1	<i>Gymnogongrus flabelliformis</i>	Antimicrobial	Sun <i>et al.</i> (2013b)
Yicathin C	<i>Aspergillus wentii</i> PT- 1	<i>Gymnogongrus flabelliformis</i>	Antimicrobial	Sun <i>et al.</i> (2013b)
Flavipesins A	<i>Aspergillus flavipes</i>	<i>Acanthus ilicifolius</i>	Antimicrobial	Bai <i>et al.</i> (2015)
3,1'-didehydro-3[2''(3''',3'''-dimethyl-prop-2-enyl)-3''-indolylmethylene]-6-methyl piperazine-2,5-dione	<i>Penicillium chrysogenum</i> MTCC 5108	Leaves of mangrove plant <i>Porteresia coarctata</i> (Roxb.)	Antimicrobial	Devi <i>et al.</i> (2012)
7-methoxymacrosporin	<i>Phoma</i> sp.	<i>Myoporum bontiodes</i> A roots	Antimicrobial	Huang <i>et al.</i> (2017)

Pyrrocidine C	<i>Lewia infectoria</i> SNB-GTC2402	<i>Besleria insolita</i>	Antimicrobial	Casella <i>et al.</i> (2013)
Biscogniazaphilones A	<i>Biscogniauxia formosana</i> BCRC 33718	Bark of a <i>Cinnamomum</i> sp.	Antimicrobial	Cheng <i>et al.</i> (2012)
Biscogniazaphilones B	<i>Biscogniauxia formosana</i> BCRC 33718	Bark of a <i>Cinnamomum</i> sp.	Antimicrobial	Cheng <i>et al.</i> (2012)
4-(2,4,7-trioxa-bicyclo[4.1.0]heptan-3-yl)-phenol	<i>Pestalotiopsis mangifera</i>	Mango tree	Antimicrobial	Subban <i>et al.</i> (2013)
6-Methyl-1,2,3-trihydroxy-7,8-cyclohepta-9,12-diene-11-one-5,6,7,8-tetralene-7-acetamide	<i>Aspergillus</i> sp.	<i>Gloriosa superba</i>	Antimicrobial	Budhiraja <i>et al.</i> (2013)
7,8-dihydronivefuranone A	<i>Microdiplodia</i> sp. KS 75-1	Stems of <i>Pinus</i> sp.	Antimicrobial	Shiono <i>et al.</i> (2012)
6(7)-dehydro-8-hydroxyterrefuranone	<i>Microdiplodia</i> sp. KS 75-1	Stems of <i>Pinus</i> sp.	Antimicrobial	Shiono <i>et al.</i> (2012)
6-hydroxyterrefuranone	<i>Microdiplodia</i> sp. KS 75-1	Stems of <i>Pinus</i> sp.	Antimicrobial	Shiono <i>et al.</i> (2012)
Nivefuranones A	<i>Microdiplodia</i> sp. KS 75-1	Stems of <i>Pinus</i> sp.	Antimicrobial	Shiono <i>et al.</i> (2012)
Crypsporioptide	<i>Cryptosporiopsis</i> sp.	Shoot tissue of shrub <i>Viburnum tinus</i>	Antimicrobial	Saleem <i>et al.</i> (2013)
Dothideomycetide A	<i>Dothideomycete</i> sp.	<i>Tiliacora triandra</i>	Antimicrobial	Senadeera <i>et al.</i> (2012)
2-Hydroxy-6-methylbenzoic acid (6-methylsalicylic acid)	<i>Pseudocercospora</i> sp. ESL 02	<i>Elaeocarpus sylvestris</i>	Antioxidant	Prihantin & Tachibana (2017)
Paclitaxel or taxol	<i>C. capsici</i>	Infected fruit of <i>Capsicum annuum</i>	Anticancer	Kumaran <i>et al.</i> (2011)
Paclitaxel or taxol	<i>Seimatoantlerium tepuiense</i>	<i>Maguireothamnus speciosus</i>	Anticancer	Strobel <i>et al.</i> (1999)
Paclitaxel or taxol	<i>Tubercularia</i> sp.	<i>T. mairei</i>	Anticancer	Wang <i>et al.</i> (2000)
Paclitaxel or taxol	<i>F. redolens</i>	Himalayan yem plants	Anticancer	Garyali <i>et al.</i> (2013)
Camptothecin	<i>E. infrequens</i>	Inner bark of <i>N. foetida</i>	Anticancer	Puri <i>et al.</i> (2005)
Camptothecin	Strain ZP5SE	Seed of <i>N. foetida</i>	Anticancer	Rehman <i>et al.</i> (2008)
Camptothecin	Strain XK001	<i>C. acuminata</i>	Anticancer	Min & Wang (2009)
Camptothecin	<i>Fusarium solani</i>	<i>C. acuminata</i>	Anticancer	Kusari <i>et al.</i> (2009)
Camptothecin	Strain 10-OH-CPT	<i>A. dimidiata</i>	Anticancer	Shweta <i>et al.</i> (2010)
Vincristine	<i>F. oxysporum</i>	<i>C. roseus</i>	Anticancer	Guo & Kunming (1998)
Vincristine and vinblastine	Strain AA-CRL-6	<i>C. roseus</i>	Anticancer	Kumar <i>et al.</i> (2013)
Vincristine and vinblastine	<i>T. radicus</i>	<i>C. roseus</i>	Anticancer	Palem <i>et al.</i> (2015)
Podophyllotoxin	Strain PPE5	Rhizomes of <i>S. peltatum</i>	Anticancer	Eyberger <i>et al.</i> (2006)

Podophyllotoxin	Strain PPE7	Rhizomes of <i>S. peltatum</i>	Anticancer	Eyberger <i>et al.</i> (2006)
Podophyllotoxin	<i>T. hirsuta</i>	<i>S. hexandrum</i>	Anticancer	Puri <i>et al.</i> (2006)
Podophyllotoxin	<i>Alternaria</i> sp.	<i>S. hexandrum</i>	Anticancer	Cao <i>et al.</i> (2007)
Podophyllotoxin	<i>F. oxysporum</i>	<i>S. recurva</i>	Anticancer	Kour <i>et al.</i> (2008)
Podophyllotoxin	<i>F. solani</i>	Roots of <i>P. hexandrum</i>	Anticancer	Nadeem <i>et al.</i> (2012)
cis-4-hydroxymellein	<i>Aspergillus flocculus</i>	<i>Markhamia platycalyx</i>	Anticancer	Tawfike <i>et al.</i> (2019)
5-hydroxymellein	<i>Aspergillus flocculus</i>	<i>Markhamia platycalyx</i>	Anticancer	Tawfike <i>et al.</i> (2019)
Dioreinol	<i>Aspergillus flocculus</i>	<i>Markhamia platycalyx</i>	Anticancer	Tawfike <i>et al.</i> (2019)
Botryoisocoumarin A	<i>Aspergillus flocculus</i>	<i>Markhamia platycalyx</i>	Anticancer	Tawfike <i>et al.</i> (2019)
Mellein	<i>Aspergillus flocculus</i>	<i>Markhamia platycalyx</i>	Anticancer	Tawfike <i>et al.</i> (2019)
Unknown	<i>Trichoderma</i> sp.	Stem bark of <i>Terminalia catappa</i>	Anticancer	Majoumouo <i>et al.</i> (2020)
(1R,6S)-3-hydroxy-4-methyl-7-oxabicyclo[4.1.0]hept-3-ene-2,5-dione (terreic acid)	<i>Pseudocercospora</i> sp. ESL 02	<i>Elaeocarpus sylvestris</i>	Antioxidant	Prihantin & Tachibana (2017)
Wentiquinone C	<i>Aspergillus</i> sp.	Marine brown alga	Antioxidant	Li <i>et al.</i> (2014)
Methyl 4-(3,4-dihydroxybenzamido)butanoate	<i>Aspergillus</i> sp.	Marine brown alga	Antioxidant	Li <i>et al.</i> (2014)
Exopolysaccharide As1-1	<i>Aspergillus</i> sp.Y16	Leave of <i>Ipomoea pes-caprae</i> (Linn.)	Antioxidant	Chen <i>et al.</i> (2011)
4,7-dihydroxy-3,9-dimethoxy-1-methylbenzo[c]chromen-6-one (graphislactone A)	<i>Cephalosporium</i> sp.	Root of <i>Trachelospermum jasminoides</i> (Apocynaceae)	Antioxidant	Song <i>et al.</i> (2005)
Phenylpropanoid amide	<i>Penicillium brasilianum</i>	Root bark of <i>Melia azedarach</i>	Antioxidant	Fill <i>et al.</i> (2010)
2-(7-hydroxy-5-methyl-1,3-dihydro-2-benzofuran-1-yl)benzene-1,3-diol (pestacin)	<i>Pestalotiopsis microspora</i>	<i>Terminalia morobensis</i>	Antioxidant	Harper <i>et al.</i> (2003)
4,7,7-trimethylbicyclo[2.2.1]heptan-3-ol (borneol)	<i>Cochliobolus nisikadoi</i>	<i>Cinnamomum camphora</i> chvar. Borneol	Antioxidant	Chen <i>et al.</i> (2011)
(2R,6aS,12aS)-1,2,6,6a,12,12a-hexahydro-2-isopropenyl-8,9-dimethoxychromeno[3,4-b] furo(2,3-h)chromen-6-one (rotenone)	<i>Penicillium</i> sp.	<i>Derris elliptica</i> Benth	Insecticidal	Hu <i>et al.</i> (2005)

Bicyclo[4.4.0]deca-1,3,5,7,9-pentaene Bicyclo[4.4.0]deca-2,4,6,8,10-pentaene (naphthalene)	<i>Muscodor vitigenus</i>	<i>Paullinia paullinioides</i>	Insecticidal	Daisy <i>et al.</i> (2012)
(E)-3-methoxy-2-propenyl-5-(2'-carbomethoxy-4'-6'-dimethoxybenzoyl)-4-pyrone (3-O-methylfunicone)	<i>Talaromyces pinophilus</i>	<i>Arbutus unedo</i>	Insecticidal	Vinale <i>et al.</i> (2017)
5-hydroxy-2-(1'-oxo-5'-methyl-4'-hexenyl) benzofuran and 5-hydroxy-2-(1'-hydroxy-5'-methyl-4'-hexenyl)benzofuran	Unidentified	<i>Gaultheria procumbens</i> L	Insecticidal	Findlay <i>et al.</i> (1997)
(2E)-5-[(3S,4S,4aR,6aS,12bS,12cS)-3-Hydroxy-4,12b,12c-trimethyl-9,10-bis(3-methyl-2-buten-1-yl)-1,2,3,4,4a,5,6,6a,7,12,12b,12c-dodecahydrobenzo[6,7]indeno[1,2-b]indol-4-yl]-2-methyl-2-pentenoic acid (nodulisporic acid A)	<i>Nodulisporium</i> sp	<i>Bontia daphnoides</i>	Insecticidal	Aly <i>et al.</i> (2011)
2,6-di-tert-butyl-p-cresol	<i>Aspergillus</i> sp.,	<i>Salvadora oleoides</i> Decne	Antidiabetic	Dhankhar <i>et al.</i> (2013)
L-783,281 (demethyl-asterriquinone B1)	<i>Pseudomassaria</i> sp.	Unknown	Antidiabetic	Zhang <i>et al.</i> (1999)
N-acetylgalactosamine (lectin)	<i>Alternaria</i> sp.	<i>Viscum album</i>	Antidiabetic	Govindappa <i>et al.</i> (2015)
Colutellin A	<i>Colletotrichum dematium</i>	<i>Pteromischum</i> sp.	Immunosuppressive	Rüegger <i>et al.</i> (1976)
Subglutinol A	<i>Fusarium subglutinans</i>	<i>Tripterygium wilfordii</i>	Immunosuppressive	Lee <i>et al.</i> (1995)
Subglutinol B	<i>Fusarium subglutinans</i>	<i>Tripterygium wilfordii</i>	Immunosuppressive	Lee <i>et al.</i> (1995)
Unknown	<i>Talaromyces wortmannii</i>	<i>Aloe vera</i>	Anti-inflammatory	Pretsch <i>et al.</i> (2014)
Mutolide	<i>Lepidosphaeria</i> sp.	Horse dung	Anti-inflammatory, Anti-arthritis	Shah <i>et al.</i> (2015)
Lovastatin	<i>Aspergillus luchuensis</i> MERV10	Marine mangrove	Anti cholesterol	Ahmed El-Gendy <i>et al.</i> (2016)
Benzene propionic acid	<i>Diaporthe arengae</i>	Twig tissue of <i>Terminalia arjuna</i>	Anti cholesterol	Patil <i>et al.</i> (2017)
3, 5-bis (1,1-dimethylethyl)-4-hydroxy methyl ester	<i>Diaporthe arengae</i>	Twig tissue of <i>Terminalia arjuna</i>	Anti cholesterol	Patil <i>et al.</i> (2017)
Pterin-6-carboxylic acid	<i>Diaporthe arengae</i>	Twig tissue of <i>Terminalia arjuna</i>	Anti cholesterol	Patil <i>et al.</i> (2017)

2,6-ditert-butyl-4-phenol	<i>Diaporthe arengae</i>	Twig tissue of <i>Terminalia arjuna</i>	Anti cholesterol	Patil <i>et al.</i> (2017)
(Z,Z)-9,12-octadecadienoic acid, n-hexadecanoic acid, acetic acid, cinnamyl ester	<i>Chaetomium globosum</i>	<i>Passiflora foetida</i>	Anti cholesterol	Kanjana <i>et al.</i> (2019)
Hexadecanoic acid, methyl ester, (Z,Z)-9,12-octadecadienoic acid	<i>Cladosporium tenuissimum</i>	<i>Memecylon edule</i>	Anti cholesterol	Kanjana <i>et al.</i> (2019)
Tetradecanoic acid, (Z,Z)-9,12-octadecadienoic acid, n-hexadecanoic acid, hexadecanoic acid, methyl ester	<i>Penicillium janthinellum</i>	<i>Justicia adhatoda</i>	Anti cholesterol	Kanjana <i>et al.</i> (2019)
Tauranin	<i>Phyllosticta spinarum</i>	<i>Platycladus orientalis</i>	Anti cholesterol	Wijetrane <i>et al.</i> (2008)

Future prospects and conclusions

Exploring the endophytic fungi-derived bioactive compounds is not without challenge, albeit it could lead to a discovery of novel compounds with various therapeutic benefits, including a resistance mechanism to counteract pathogenic infiltration. It is believed that secondary metabolites synthesized from endophytic microbes offer a competitive option in overcoming the drug resistance issues by bacteria. Therefore, researchers need to improve and develop the isolation method, rapid genomic data extraction and sequence pairing, which will assist in identifying the types of endophytes as well as their diversity and therapeutic benefit. The toxicity clarification of the identified drug, either on humans, animals, or the environment, is also essential in meeting a highly effective drug for multiple diseases nowadays. Another challenge that needs to be taken into account is the large-scale production of the targeted drugs since there are a number of genes involved in the biosynthesis pathway. The exploitation of these challenges holds a great promise for human's health. There is an increasing concern on applying endophytic-based natural products in the industrial sector. In this review, some of the reported compounds such as paclitaxel or taxol, camptothecin, vinblastine, vincristine and statin have been penetrated in the market for pharmaceutical and medicinal uses. A triumphant impact of these endophytic fungal-based drugs has given a positive indicator for the researchers in finding a novel compound, which may benefit other industrial sectors, including agriculture, food safety and cosmetics.

ACKNOWLEDGEMENTS

We would like to thank Malaysia Ministry of Higher Education (MOHE) for supporting the project of endophytic fungi (PRGS/1/2019/STG05/UNIKL/02/1).

CONFLICT OF INTERESTS

The authors have declared that no conflict of interest exists.

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